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In association with

Otto L. Mohr
Professor of Anatomy, Oslo

Tage Kemp
Professor of Human Genetics, Copenhagen

edited by:

Gunnar Dahlberg
Head of the State Institute of Human Genetics and Race Biology, Uppsala

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Department of Sociology and Anthropology
University of Kansas, Lawrence, Kan., U.S.A.

A PROPOSED METHODOLOGY FOR DISCERNING THE MOST IMPORTANT VARIABLES AFFECTING BLOOD PRESSURE[1]

With especial reference to the effect of age, weight groups, body build, urban or rural life, nutrition, climate, and intestinal parasites on blood pressure in Puerto Rico

By RUPERT IVAN MURRILL

Contents

[1] This paper is part of a larger study entitled "Racial Blood Pressure Studies. A Critique of Methodology. With Special Reference to the Effect of Age, Nutrition, Climate and Race on Blood Pressure in Puerto Rico", first published in the Proceedings of the American Philosophical Society, Vol. *99*, No. 4, 1955.

Introduction

In order to evaluate correctly existing blood pressure studies, from the point of view of methodology, it will first be necessary to use a representative sample of a particular population, in this case the population of Puerto Rico.

The necessity for using a truly representative sample of a large population, regarding blood pressure, is quite simple. First, until this study, such a representative sample has not been obtained. Second, only from such a sample can one design the proper experiments by which to test the importance of different variables possibly affecting blood pressure.

Scope

This study is not concerned specifically with hypertension, arteriosclerosis or arteriolosclerosis.

It is concerned with the methodology involved in discerning the most important variables affecting blood pressure, based on a representative male and female Puerto Rican sample. This study will indicate the range of normal blood pressure of the 1948 Puerto Rican population, particularly ages 20–49, with due regard for such variables as sex, age, weight groups, etc. It will be shown that the most important variables affecting blood pressure are weight groups and possibly age in relation to weight groups, and that the following variables exert no appreciable effect on blood pressure:—body build, urban or rural life, nutritional class, the climate of two main Puerto Rican regions, and intestinal parasitic infestation.

Background and acknowledgements

The Puerto Rican portion of this study is part of a larger human biological study, in which the author participated, made between June, 1948, and February, 1949, of the adult Puerto Rican population. The larger study included 26 anthropometric measurements, a dental analysis, blood typing, and several other physiological evaluations including blood pressure.

The Puerto Rican project was originally conceived mainly by Professor *Harry Shapiro* of Columbia University and the American Museum of Natural History, who proposed to the Social Science Research Center of the University of Puerto Rico that a combined human biological and cultural investigation should be followed.

Professor *Julian Steward*, at that time of Columbia University, was invited to take charge of the cultural aspect of the project, mainly community studies, by Professor *Shapiro* who subsequently directed the human biological aspect. Thus the whole project was eventually the result of the combined efforts of the Social Science Research Center of the University of Puerto Rico, the American Museum of Natural History, and the Department of Anthropology of Columbia University.

Concerning the human biological aspect of the project it was also Professor *Shapiro* who suggested that the Puerto Rican population be sampled in a structured fashion. The results of this suggestion are described in detail in this study under the heading "Sample Structure".

In addition to Professors *Shapiro* and *Steward* the author wishes to thank the many individuals in Puerto Rico who aided the project in countless way, and without whose aid the project would never have been completed. In particular the author would like to thank Dr. *Pons*, Director of the Department of Public Health, Dr. *Morales Otero* of the School of Tropical Medicine, Dr. *Janer*, Chief of the Bureau of Registry and Vital Statistics, Dr. *Rotenberg*, formerly Head of the Social Science Research Center, Dr. *Lydia Roberts* of the Department of Nutrition of the University of Puerto Rico, and last but not least the doctors who were in charge of the various public health centers or hospitals where individuals were obtained for the Puerto Rican sample.

Grateful thanks are also due to the Directors of the Watson Scientific Computing Laboratory of the International Business Machines Corporation near Columbia University, who made available to the project the necessary IBM machines for the statistical analysis of the Puerto Rican data.

Finally, the author is greatly indebted to the Wenner-Gren Foundation for Anthropological Research for a pre-doctoral fellowship, without which the Puerto Rican analysis would not have been possible.

Puerto Rico

Puerto Rico is an island which lies east of Santo Domingo in the West Indies. It is roughly rectangular in shape, approximately 113 miles long, and averages 45 miles in width.

Puerto Rico has a mountainous backbone, rising 4000 feet in height, running from west to east in the central part of the island.

From the point of view of climate Puerto Rico may be divided into seven main regions each containing a varying number of municipios or municipalities.

These regions correspond to the seven regions of the 1940 Census of Population and Housing. The regions are doubtless an oversimplification of existing climatic and ecological zones but are sufficiently distinctive for the purposes of this study. The regions are shown in fig. 1 and are as follows:—

Region 1. North Western Coast. Arid.
2. North Central Coast. Subhumid to humid.
3. Eastern Coast. Humid.
4. Southern Coast. Semi-arid to very arid.
5. Western Coast. Wet summer and dry winter.
6. Western Mountainous Interior. Rainy and humid.
7. Eastern Mountainous Interior. Humid.

Coffee is grown in region 6 and tobacco in region 7. Sugar cane is grown predominantly in regions 1–5. However, the most diversified agriculture is to be found in regions 1 and 2, for here one encounters in addition to sugar cane, cotton and tobacco in the northwest; coconut, grapefruit, and pineapple plantations east of Arecibo; and the best organized dairy district near San Juan and Rio Piedras. Furthermore, San Juan is the largest urban area in the island with the most important commercial and manufacturing enterprises.

The mean temperature for the whole island is 73° F in winter and 79° F in summer, with an average of 76.6° F. The average annual rainfall is 72.6 inches, the lowest readings being in region 4 and the highest in region 6 and the municipio of Luquillo. The average annual hours of sunshine is 2847 in San Juan, thus there is a high level of solar ultra-violet radiation. The mean barometric pressure at San Juan is 29.90 inches, and the mean relative humidity is 78% at 9 a.m., 76% at 12 noon, and 80% at 9 p.m. Therefore, one sees no sudden changes in temperature, a stable barometric pressure and a fairly high humidity.

The original Indian population of Puerto Rico was rapidly subjugated by the Spanish and to all intents and purposes disappeared perhaps as early as 1544. In 1815 foreigners were invited to settle on the island being offered free land and trade, citizenship, and permission to bring negro slaves, although the latter were first introduced in 1510. Immigrants came from the French and English Antilles, Haiti, Santo Domingo, and Venezuela. In 1873 the negro

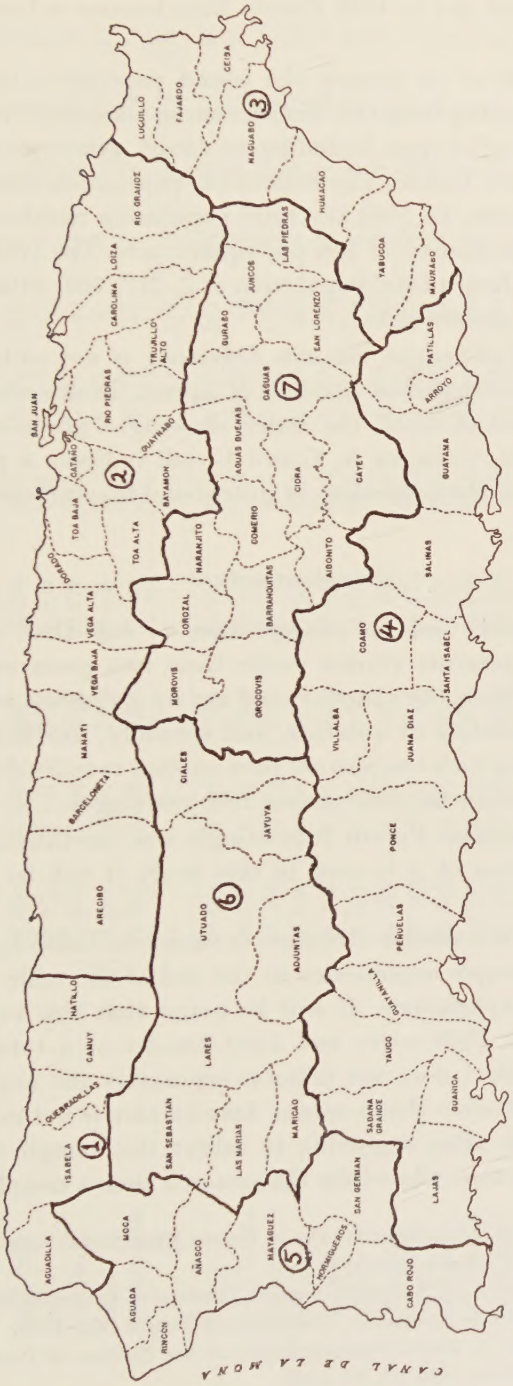

Fig. 1. Puerto Rico. Regions. 1 = Northwestern Coast, 2 = North Central Coast, 3 = Eastern Coast, 4 = Southern Coast, 5 = Western Coast, 6 = Western Interior, 7 = Eastern Interior.

slaves were freed and in 1898 Puerto Rico became a United States possession.

As a result of its history the island population is a heterogeneous one varying from the Mediterranean Caucasoid to the West African Negro racial type, including no doubt, genotypically speaking, the American Indian. The bulk of the population shows various degrees of mixture. In 1940 the total population numbered 1, 869, 255 with a high density of 546 per square mile. The available 1950 Census figures show a total population of 2, 210, 703, with a density now of 645 per square mile.

Although full-fledged vitamin deficiency is not widespread in Puerto Rico, nevertheless studies of sprue, hookworm, ascaris, schistosoma, and of diets, the latter showing a grave scarcity of protein, calcium, vitamins A, C and G—all indicate a population living near or on the borderline of nutritional insufficiency[1, 2].

Sample structure

It is probably not an exaggeration to say that almost all existing blood pressure studies suffer from two gross and fundamental errors. First, the samples used are by no means representative of the population in question, and secondly, unreliable standards derived from such samples are then applied to individuals. I had occasion to mention the first error a few years ago[3].

Since the original Puerto Rico sample was carefully calculated and a modification of it is used in this study it will be described at some length.

The calculated sample structure is shown in Table 1, and with the aid of the sample explanation at the end of the table the latter should be self-explanatory. It will be noted that this sample was designed to give 2500 males and 2500 females or a total of 5000 individuals. Table 1 does not indicate separately the negro breakdown since the Puerto Rican census data on race is not reliable.

A few weeks after beginning to collect this sample it became clear that in the time alloted for the research such a sample was too

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[1] *Blanco, Ana T.:* Nutrition Studies in Puerto Rico. Social Science Research Center, University of Puerto Rico 1946.

[2] *Roberts, Lydia J.*, and *Rosa L. Stefani:* Patterns of Living in Puerto Rican Families. Dept. of Home Economics, University of Puerto Rico 1949.

[3] *Murrill, R. I.:* A Blood Pressure Study of the Natives of Ponape Island, Eastern Carolines. Hum. Biol. *21*, 47, 1949.

Table 1. Sample structure

Region	Municipio	1940 Total Popn	1940 Popn 20–44	1940 20–44 %	1948 Total Popn	1948 Popn % Urban	1948 Popn 20–44	SAMPLE Total	Urban M	Urban F	Rural M	Rural F
A	B	C	D	E	F	G	H	I	J	K	L	M
1	Aguadilla	34 956	12 643	36.1	42 004	42.6	15 193	103	22	22	29	30
	Camuy	18 922	6 161	32.5	21 513	13.5	7 005	47	3	3	20	21
	Hatillo	18 322	5 910	32.2	20 276	15.2	6 535	44	3	3	19	19
	Isabela	25 842	8 291	32.0	26 670	17.3	8 556	57	4	5	24	24
	Quebradillas	11 494	3 732	32.4	12 545	12.9	4 073	27	1	2	12	12
								278	33	35	104	106
2	Arecibo	69 192	24 390	35.2	80 957	45.6	28 537	192	44	44	52	52
	Barceloneta	18 545	6 175	33.3	20 768	9.5	6 916	46	2	2	21	21
	Bayamon	37 190	12 463	33.5	46 783	34.1	15 677	105	18	18	34	35
	Carolina	24 046	7 724	32.1	29 200	19.3	9 379	63	6	6	25	26
	Catano	9 719	3 535	36.3	12 392	80.5	4 507	30	11	11	4	4
	Dorado	9 481	3 128	32.9	11 038	18.0	3 641	24	2	2	10	10
	Guaynabo	18 319	6 246	34.1	24 222	4.2	8 260	55	1	1	26	27
	Loiza	22 145	7 115	32.1	24 430	35.3	7 849	53	9	10	17	17
	Manati	29 366	9 501	32.3	32 587	13.0	10 542	71	4	5	31	31
	Rio Grande	16 116	5 126	31.8	16 800	15.5	5 344	36	3	2	15	16
	Rio Piedras	68 290	26 374	38.6	99 026	57.1	38 244	257	73	74	54	56
	San Juan	169 247	69 543	41.0	230 231	100.0	94 601	635	315	320	—	—
	Toa Alta	13 371	4 138	30.9	14 075	7.2	4 356	29	1	1	13	14
	Toa Baja	11 410	3 880	34.0	13 787	17.3	4 689	32	2	3	14	13
	Trujillo Alto	11 726	3 595	30.6	13 747	7.0	4 215	28	1	1	13	13
	Vega Alta	14 329	4 381	30.5	15 978	20.8	4 884	33	3	4	13	13
	Vega Baja	23 105	7 441	32.2	23 358	29.4	7 524	51	7	8	18	18
								1 740	502	512	360	366

Table 1. Sample structure (cont.)

Region	Municipio	1940 Total Popn	1940 Popn 20–44	1940 20–44 %	1948 Total Popn	1948 Popn % Urban	1948 Popn 20–44	SAMPLE Total	Urban M	Urban F	Rural M	Rural F
A	B	C	D	E	F	G	H	I	J	K	L	M
3	Ceiba	7 021	2 186	31.1	5 523	19.7	1 720	12	1	1	5	5
	Culebra	860	229	26.6	738	—	197	—				
	Fajardo	20 405	7 044	34.5	24 324	34.8	8 397	56	10	10	18	18
	Humacao	29 833	10 731	35.9	32 220	19.0	11 590	78	8	7	31	32
	Luquillo	8 851	2 787	31.4	10 009	21.7	3 152	21	3	2	8	8
	Maunabo	10 792	3 444	31.9	11 548	9.4	3 685	25	1	1	12	11
	Naguabo	19 180	6 376	33.2	17 352	24.9	5 768	39	5	5	15	14
	Vieques	10 362	3 266	31.5	10 981	22.0	3 461	24	2	3	10	9
	Yabucoa	27 438	9 256	33.7	33 100	15.8	11 165	75	6	6	32	31
								330	36	35	131	128
4	Arroyo	10 746	3 855	35.8	13 609	29.3	4 882	33	5	5	12	11
	Coamo	22 772	7 567	33.2	25 340	42.2	8 420	57	12	12	17	16
	Guanica	12 685	4 292	33.8	14 739	32.0	4 988	34	6	5	11	12
	Guayama	30 511	11 437	37.4	36 123	51.2	13 539	91	24	23	22	22
	Guayanilla	15 577	5 460	35.0	16 941	16.5	5 938	40	4	3	16	17
	Juana Diaz	23 396	8 512	36.3	28 540	21.8	10 383	70	8	7	27	28
	Lajas	14 736	4 844	32.8	16 883	19.0	5 549	37	4	3	15	15
	Patillas	17 319	5 669	32.7	20 358	11.2	6 663	45	3	2	20	20
	Penuelas	14 789	4 880	33.0	15 608	9.8	5 151	35	1	2	17	15
	Ponce	105 116	39 705	37.7	119 087	61.6	44 979	298	91	93	59	55
	Sabana Grande	14 146	4 746	33.5	17 105	35.3	5 739	39	7	7	13	12
	Salinas	19 400	7 278	37.5	21 599	55.0	8 104	54	15	15	12	12
	Santa Isabel	11 468	4 499	39.2	13 889	20.9	5 449	37	4	4	15	14
	Villalba	12 871	4 103	31.8	12 878	41.0	4 106	28	6	5	8	9
	Yauco	30 533	10 389	34.0	31 329	34.8	10 661	72	13	12	23	24
								970	203	198	287	282

Table 1. Sample structure (cont.)

Region	Municipio	1940 Total Popn	1940 Popn 20–44	1940 20–44 %	1948 Total Popn	1948 Popn % Urban	1948 Popn 20–44	SAMPLE				
								Total	Urban M	Urban F	Rural M	Rural F
A	B	C	D	E	F	G	H	I	J	K	L	M
5	Aguada	17 923	5 957	33.2	20 129	11.9	6 691	45	2	3	20	20
	Anasco	15 701	5 235	33.3	16 030	23.3	5 344	36	4	4	14	14
	Cabo Rojo	28 586	9 081	31.7	33 398	19.3	10 611	71	7	7	28	29
	Hormigueros	6 098	2 153	35.3	6 856	35.2	2 421	16	3	3	5	5
	Mayaguez	76 487	28 169	36.8	89 494	67.9	32 961	222	75	76	36	35
	Moca	19 716	6 378	32.3	19 235	19.7	6 222	42	4	4	17	17
	Rincon	9 256	2 852	30.8	10 977	17.8	3 382	23	2	2	9	10
	San German	26 473	9 253	34.9	28 757	23.5	10 051	67	8	8	25	26
								522	105	107	154	156
6	Adjuntas	22 556	7 479	33.1	28 354	21.9	9 402	63	7	7	25	24
	Ciales	22 906	6 917	30.2	22 134	9.4	6 684	44	2	2	20	20
	Jayuya	14 589	4 728	32.4	15 838	32.6	5 133	34	5	6	12	11
	Lares	29 914	9 276	31.0	30 973	20.6	9 605	65	7	6	26	26
	Las Marias	9 626	2 947	30.6	10 544	19.8	3 229	22	2	2	9	9
	Maricao	7 724	2 537	32.8	8 141	18.1	2 674	18	2	1	7	8
	San Sebastian	30 266	9 622	31.7	36 197	14.1	11 507	77	6	5	33	33
	Utuado	42 531	13 514	31.7	40 968	5.4	13 016	88	2	3	42	41
								411	33	32	174	172

Table 1. Sample structure (cont.)

Region	Municipio	1940 Total Popn	1940 Popn 20–44	1940 20–44 %	1948 Total Popn	1948 Popn % Urban	1948 Popn 20–44	SAMPLE Total	Urban M	Urban F	Rural M	Rural F
A	B	C	D	E	F	G	H	I	J	K	L	M
7	Aguas Buenas	14 671	4 470	30.4	14 817	14.2	4 514	30	2	2	13	13
	Aibonito	16 819	5 520	32.8	16 320	27.7	5 356	36	5	5	13	13
	Barranquitas	17 096	5 319	31.1	18 829	10.8	5 858	39	2	2	18	17
	Caguas	53 356	18 700	35.0	62 439	44.4	21 885	147	34	31	40	42
	Cayey	31 391	10 672	34.0	32 965	14.9	11 208	75	6	5	32	32
	Cidra	20 392	6 385	31.3	20 116	13.3	6 298	42	3	3	18	18
	Comerio	18 539	5 887	31.7	20 696	17.5	6 571	44	4	4	18	18
	Corozal	20 458	6 105	29.8	23 484	9.9	7 008	47	2	3	22	20
	Gurabo	15 870	4 964	31.2	16 352	25.6	5 115	34	5	4	12	13
	Juncos	19 464	6 692	34.3	19 503	20.0	6 705	45	4	5	19	17
	Las Piedras	15 389	4 761	30.9	16 076	13.0	4 974	33	2	2	15	14
	Morovis	19 167	5 870	30.6	18 367	13.2	5 626	38	2	3	17	16
	Naranjito	13 954	4 186	30.0	15 300	11.0	4 590	32	2	2	14	14
	Orocovis	19 770	6 040	30.5	22 226	8.0	6 790	46	2	2	21	21
	San Lorenzo	26 627	8 324	31.2	28 947	17.1	9 049	61	5	5	26	25
								749	80	78	298	293
	TOTALS											
1	Region	109 536	36 737	33.5	123 008	24.4	41 362	278	33	35	104	106
2	Region	565 597	204 755	36.2	709 379	58.2	259 165	1 740	502	512	360	366
3	Region	134 742	45 319	33.6	145 795	21.5	49 135	330	36	35	131	128
4	Region	356 065	127 236	34.8	404 028	41.3	144 551	970	203	198	287	282
5	Region	200 240	69 078	34.5	224 876	40.6	77 683	522	105	107	154	156
6	Region	180 112	57 020	31.6	193 149	15.8	61 250	411	33	32	174	172
7	Region	322 963	103 895	32.1	346 437	21.0	111 547	749	80	78	298	293
	PUERTO RICO	1 869 255	644 040	34.4	2 146 672	39.7	744 693	5 000	992	997	1 508	1 503

Table 1. Sample explanation (cont.)

A Census region, from 1940 Census, Puerto Rico, Bulletin No. 3.
B Municipios in each census region.
C Total population, by municipio, 1940 Census, Puerto Rico, Bulletin No. 2, Table 16.
D Population ages 20–44, by municipio, 1940 Census, Puerto Rico, Bulletin No. 2, Table 18.
E D divided by C, multiplied by 100, taken to one decimal place.
F Estimate made by the Bureau of Registry and Vital Statistics of the Department of Health, Government of Puerto Rico for July 1, 1948, based on an arithmetic extrapolation from the census of December 1, 1935, and April 1, 1940.
G Per cent urban, obtained from same source as F, taken to one decimal place.
H Per cent from E applied to F. See *F. P. Bartlett* and *B. Howell*, "Puerto Rico and its Population Problem", Government of Puerto Rico, 1946, Graph 16.
I Sample total, 1948, ages 20–44, apportioned by municipio to give a total sample of 5000. Obtained by dividing municipio figure, column H, by Puerto Rico total column H, and multiplying by 5000.
J and K Total of J and K equals per cent from G applied to I.
L and M Total of L and M equals I minus total of J and K.

The Male-female breakdown of each municipio sample is based on the 1940 sex ratio, ages 20–44, for each census region with a predetermined assumption that a total of 2500 or 50 per cent of the total sample would be of each sex. The calculations are as follows.

Region	1940 20–44 M	1940 20–44 F	1940 % of Total M	1940 % of Total F	1940 Ratio M/F (1)	1948 Region Sample (2)	Excess (1)×(2) M	Excess (1)×(2) F	1948 Sample M	1948 Sample F
1	18 123	18 614	5.645	5.762	979.6	278	—	2.72	137	141
2	100 977	103 788	31.456	32.129	979.0	1740	—	17.03	862	878
3	23 703	21 616	7.383	6.691	1103.4	330	3.64	—	167	163
4	63 702	63 534	19.844	19.667	1008.9	970	9.78	—	490	480
5	33 645	35 433	10.481	10.968	955.5	522	—	4.98	259	263
6	28 669	28 351	8.930	8.776	1017.5	411	4.18	—	207	204
7	52 188	51 707	16.257	16.006	1015.6	749	7.60	—	378	371
	321 007	323 033				5000			2500	2500

M F (1) is not a sex ratio but a factor from the 1940 census to be applied to the 1948 region sample to get the difference in number of each sex for the region. For example:—Region 2 total sample equals 1740. Excess females equal 17.03. Dividing 1740 by 2 equals 870 (if males equalled females). Divide excess by 2 (17.03/2), which equals 8.5. Subtract 8.5 from 870, which equals 861.5. Also add 8.5 to 870, which equals 878.5. The figures used were 862 males and 878 females. The males and females must equal the region sample, i.e.:—1740. Finally the municipio male-female sample, urban and rural, was adjusted so that the totals would match the regional figures previously determined.

Table 2. Calculated compared to actual sample

Region	Municipio	Male		Female	
		Calculated	Actual	Calculated	Actual
1	Aguadilla	34	37	35	34
	Camuy	15	13	16	14
	Hatillo	15	6	15	7
	Isabela	18	11	19	10
	Quebradillas	9	18	9	16
		91	85	94	81
2	Arecibo	64	108	64	70
	Barceloneta	15	14	15	7
	Bayamon	35	54	35	17
	Carolina	21	103	21	70
	Catano	10	8	10	2
	Dorado	8	16	8	—
	Guaynabo	18	27	19	3
	Loiza	17	73	18	36
	Manati	23	38	24	21
	Rio Grande	12	21	12	9
	Rio Piedras	85	32	87	47
	San Juan	210	201	214	184
	Toa Alta	9	16	10	6
	Toa Baja	11	21	11	6
	Trujillo Alto	9	2	9	4
	Vega Alta	11	35	11	25
	Vega Baja	17	36	17	23
		575	805	585	530
3	Ceiba	4	6	4	2
	Culebra	—	2	—	1
	Fajardo	19	35	19	26
	Humacao	26	35	26	30
	Luquillo	7	2	7	4
	Maunabo	9	5	8	7
	Naguabo	13	15	13	6
	Vieques	8	4	8	1
	Yabucoa	25	16	24	8
		111	120	109	85
4	Arroyo	11	10	11	12
	Coamo	20	13	19	8
	Guanica	11	11	11	1
	Guayama	31	29	30	52
	Guayanilla	13	2	13	—
	Juana Diaz	24	18	23	23
	Lajas	13	13	12	5
	Patillas	15	15	15	26
	Penuelas	12	8	11	11
	to bring forward	150	119	145	138

Table 2. Calculated compared to actual sample (cont.)

Region	Municipio	Male		Female	
		Calculated	Actual	Calculated	Actual
	brought forward	155	119	145	138
	Ponce	100	90	99	107
	Sabana Grande	13	14	13	4
	Salinas	18	13	18	9
	Santa Isabel	13	4	12	5
	Villalba	9	19	9	24
	Yauco	24	24	24	3
		327	283	320	290
5	Aguada	15	17	15	18
	Anasco	12	19	12	9
	Cabo Rojo	23	29	24	14
	Hormigueros	5	5	5	6
	Mayaguez	74	99	74	100
	Moca	14	5	14	7
	Rincon	7	3	8	3
	San German	22	21	23	10
		172	198	175	167
6	Adjuntas	22	13	21	14
	Ciales	15	23	15	17
	Jayuya	11	6	11	7
	Lares	22	25	22	29
	Las Marias	7	11	7	12
	Maricao	6	9	6	3
	San Sebastian	26	26	25	27
	Utuado	29	30	29	35
		138	143	136	144
7	Aguas Buenas	10	12	10	7
	Aibonito	12	11	12	9
	Barranquitas	13	10	13	12
	Caguas	49	72	48	64
	Cayey	25	29	24	27
	Cidra	14	13	14	12
	Comerio	15	16	15	13
	Corozal	16	16	15	10
	Gurabo	11	4	11	3
	Juncos	15	5	15	3
	Las Piedras	11	9	11	2
	Morovis	13	19	13	12
	Naranjito	11	13	11	11
	Orocovis	16	15	16	8
	San Lorenzo	21	25	20	15
		252	269	248	208
	TOTALS	1666	1903	1667	1505

Table 3. Region distribution of sample

Region	Male				Female			
	Calculated		Actual		Calculated		Actual	
	No.	%	No.	%	No.	%	No.	%
1	91	5.5	85	4.5	94	5.6	81	5.4
2	575	34.5	805	42.3	585	35.1	530	35.2
3	111	6.7	120	6.3	109	6.5	85	5.6
4	327	19.6	283	14.9	320	19.2	290	19.3
5	172	10.3	198	10.4	175	10.5	167	11.1
6	138	8.3	143	7.5	136	8.2	144	9.6
7	252	15.1	269	14.1	248	14.9	208	13.8
TOTALS	1666	100.0	1903	100.0	1667	100.0	1505	100.0

large. Accordingly a decision was made to obtain a sample two thirds as large as the original one, namely a total of 3333 individuals. Table 2 indicates the new male and female calculated sample by region and municipio, the urban and rural figures being added together. Table 2 also shows the actual numbers obtained.

Table 3 is a percentage summary of Table 2 by region. Region 2 in the male actual sample is overloaded. This is largely due to the fact that region 2 was the first region worked in when the originally calculated male sample was supposed to be 2500. However San Juan in region 2 is the largest urban center and is a pool supplied from all the island regions, as is doubtless the area between Vega Alta and Carolina, hence any excess individuals obtained in this part of region 2 probably does not materially alter the representativeness of the total actual sample. The calculated and actual female samples

Table 4. Age distribution of sample

Ages	Male				Female			
	1940 Popn.		1948 Sample		1940 Popn.		1948 Sample	
	No.	%	No.	%	No.	%	No.	%
17–19	*61483	13.7	92	4.8	*64648	14.5	71	4.7
20–24	102464	22.8	588	30.9	103862	23.2	452	30.0
25–29	72263	16.1	418	22.0	75745	17.0	315	20.9
30–34	52012	11.6	300	15.8	50584	11.3	239	15.9
35–39	50529	11.2	227	11.9	50609	11.3	251	16.7
40–44	43739	9.7	171	9.0	42233	9.5	103	6.8
45–49	36186	8.1	84	4.4	32816	7.3	57	3.8
50–54	30639	6.9	23	1.2	26352	5.9	17	1.1
	449315	100.0	1903	100.0	446849	100.0	1505	99.9

* Approximate figure. Census data not available for this age group.

Table 5. Urban-rural distribution of sample

Region	Male				Female			
	Calculated %		Actual %		Calculated %		Actual %	
	Urban	Rural	Urban	Rural	Urban	Rural	Urban	Rural
1	25.0	75.0	23.5	76.5	24.5	75.5	16.0	84.0
2	58.1	41.9	34.2	65.8	58.3	41.7	40.6	59.4
3	21.6	78.4	37.5	62.5	21.1	78.9	48.2	51.8
4	41.9	58.1	44.5	55.5	41.3	58.7	51.7	48.3
5	40.7	59.3	48.0	52.0	40.3	59.7	49.7	50.3
6	15.3	84.7	21.7	78.3	15.4	84.6	23.6	76.4
7	20.4	79.6	42.0	58.0	21.1	78.9	49.0	51.0
TOTAL	39.7	60.3	37.0	63.0	39.8	60.2	42.4	57.6

by region are remarkably close. The total figure of 1505 females in the actual sample is due to the elimination of females who were pregnant, or had no blood pressure recorded, or were 55 years of age and over.

Table 4 shows the age distribution of the actual sample compared to the 1940 census figures. The reason for the inclusion of individuals 17–19 and 45–54 years of age is because we did not choose individuals primarily on the basis of age. Our first endeavor was to get municipio and region representation.

Table 5 indicates the calculated and actual sample urban and rural percentages. Again subjects were not chosen primarily for urban or rural residence. Especially in the smaller regions one can expect random variation to account for differences. Of greater importance is that the total urban-rural percentages are close. For the total actual sample the male plus female urban percentage is 39.4 and the rural 60.6. It is of some interest to observe that the obtainable 1950 Census figures show that the male plus female urban percentage for the whole of Puerto Rico is 40.5 and the rural is 59.5.

As a further piece of evidence and an important one concerning the actual sample, I can cite an interesting experiment conducted by Dr. *Thieme*, my colleague on this research project. In a study on Puerto Rican blood types[1] where he calculated the ABO and Rh frequencies for those individuals typed in the actual sample, he states, "Because those not typed were not randomly spread through the sample, or not random by municipio, the blood type sample is not as accurately representative of the total population as the

[1] *Thieme, F. P.* The Geographic and Racial Distribution of ABO and Rh Blood Types and Tasters of PTC in Puerto Rico. Amer. J. hum. Genet. *4*, 94, 1952.

Table 6. Comparison of total actual sample with total calculated sample for frequencies of ABO and Rh types

	ABO						
	No.	O	A_1	A_2	B	A_1B	A_2B
Calculated	3333	53.88	24.88	9.70	9.49	1.01	1.04
Actual	3245	53.99	24.84	9.61	9.52	0.99	1.05
Difference*		+.11	—.04	—.09	+.03	—.02	+.01

	Rh								
	No.	rh	rh′	rh″	rh′rh″	Rh_o	Rh_1	Rh_2	Rh_1Rh_2
Calculated	3333	8.53	1.16	0.46	0.11	12.82	48.75	15.46	12.71
Actual	2528	8.78	1.23	0.47	0.12	13.21	48.89	14.79	12.50
Difference*		+.25	+.07	+.01	+.01	+.39	+.14	—.67	—.21

* None of the differences shown is significant.

calculated sample. However, when the municipios are combined into regional districts, as has been done, no one section of the island is insufficiently represented in the final sample". Despite the latter part of this statement, *Thieme* calculated the frequencies in a corrected sample designed to give the exact proportions of the calculated sample, and compared those frequencies with the actual ones. This comparison is shown in Table 6. There are no significant differences.

It is not claimed that the actual sample used in this study, in regard to the categories mentioned, is absolutely representative of the total population. The only way to obtain a completely representative sample is to take the entire population, obviously an unfeasible task when the population is very large. What is claimed here is that an attempt was made to obtain as representative a sample as possible of the male and female population of Puerto Rico, ages 20–44, and that no known bias favored any one segment of the population. Furthermore, the sample used here is immeasurably more representative of the Puerto Rican population than blood pressure samples, cited in the literature, are of other populations. One has only to examine the latter samples to observe the truth of this remark.

Method

1. Each individual in the actual sample was first questioned regarding age, occupation, urban or rural residence, and duration in years of residence in the municipio. A series of special questions,

based on *Roberts*'[1] pre-published data, were then asked in order to place the individual in one of the four main nutritional classes. The latter are described in some detail under the heading "General Analysis of Puerto Rican Blood Pressures", Section F. The basic assumption made here is that since Puerto Rican food habit patterns are very strong, and assuming further that no marked increase of income had occurred, then the dietary pattern as stated by individuals at the time of questioning, or their present age, was the same as it had always been prior to the time of questioning.

2. After the individual had been questioned, a series of anthropometric measurements were made. Next, the individual was seated and a dental examination was made and temperature taken. The blood pressure was then taken, some ten minutes after the individual had been seated. The individual's arm rested on a table at about heart level. One reading was taken by the auscultatory method, always on the right arm, using a Tycos aneroid sphygmomanometer with a 12 cm arm band. The systolic reading was taken at the appearance of the first sound and the diastolic at the point at which sounds become dull and muffled[2].

3. The Puerto Rican population being a heterogeneous one an attempt was made to sort the population into phenotypically similar groups. An "ethnic factor" was devised using, in descending order of importance, the criteria of skin color, hair form, nose shape or width and lip thickness. The "ethnic factor" was calculated in the following manner.

1. Skin color was compared with the *von Luschan* skin color scale. Recorded values ranged from 7–32 with a mean value of 16 for the total sample.
2. Hair form was recorded on a 5-point scale using the values 0, 4, 6, 12 or 16-hair form thus contributing approximately one half of the value of skin color in the "ethnic factor" total.

3 and 4. Nose shape and lip thickness were recorded also on a 5-point scale, using the values 0, 2, 4, 6 or 8—thus these characteristics contributed approximately one half of the value of hair form.

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[1] *Roberts*, op. cit.

[2] Standard Method for Taking and Recording Blood Pressure Readings. J. Amer. med. Ass. *113*, 294, 1939.

By adding the values of the four phenotypic characteristics a total of 7–64 was possible, the low number presumably representing the extreme White phenotype and the high number the extreme Negro phenotype. The range of possible values 7–64 was divided into 10 groups (0–9 inclusive), each individual being assigned to one group. As *Thieme* States[1], "Inasmuch as the characters used are those most variable in a Negro-White mixed population, they do indicate the general racial affinities of the groups—it is assumed that within any one of these 'ethnic groups' the genetic homogeneity is probably greater than in any combination of these groups, and certainly greater than in a combination of extreme groups."

4. The tedious statistical calculations in this study were done and checked by the author mainly on IBM machines at the Watson Scientific Computing Laboratory of the International Business Machines Corporation. The standard error is used in preference to the probable error. In testing for significance of difference a t value of 2.58 or a significance at the 1% level of confidence was originally decided upon for use throughout this study. The main reason for using such a rigorous test is that the methodological approach to *blood pressure* differences in this study is for the most part new. Furthermore it is the author's opinion that many blood pressure differences cited in the literature as significant are spurious precisely because of the lack of rigorousness of the statistical test.

5. At this point it must be mentioned that the blood pressure readings were taken by two of my colleagues. Dr. *Fred Thieme* and Miss *Joanne Finkle*. As this introduces the factor of personal error in measurement, sub-samples were devised to test the significance of difference between the observers.

The technique used to obtain the personal error sub-sample was as follows. Those males whose blood pressure was measured by *Finkle* were first sorted out. These were shuffled and every fourth individual was selected to obtain a sample of 200. The variables considered to be important were age, region, nutritional class and ethnic group. Each age group was then analysed in regard to the different regions (1–7) and the latter in regard to the number of individuals who were of a particular nutritional class (1–4) who in turn were of a particular ethnic group (0–8, few individuals in the total sample fell into ethnic group 9). The males measured by *Thieme* were then shuffled and by random sorting were matched regarding

[1] Thieme, op. cit.

the above variables, with *Finkle*'s males. We may call this test sample A, male. Exactly the same procedure was used for the females, resulting in a second sample which we may call test sample B, female.

For testing the significance of difference in all *matched* samples in this study the formulae used for determining the significance of difference between matched samples are as follows: Let D_{sys} and D_{dias} represent the difference in the systolic and diastolic scores. Then ΣD_{sys} N and ΣD_{dias} N will equal the mean systolic and diastolic difference. Let the latter be represented by the symbols $M_{D\,sys}$ and $M_{D\,dias}$. Also let $\sigma_{D\,sys}$ represent the standard deviation of the systolic difference which equals $\sqrt{\Sigma (D_{sys}^2)\ N - \Sigma (D_{sys})^2}$, N, and let $\sigma_{D\,dias}$ represent the diastolic difference standard deviation.

The standard error of the mean systolic and diastolic difference may be represented by $\sigma_{MD\,sys}$ and $\sigma_{MD\,dias}$, which equal $\sigma_{D\,sys}/\sqrt{N}$ and $\sigma_{D\,dias}\ \sqrt{N}$. t_{sys} or t_{dias} is then found by $M_{D\,sys}/\sigma_{MD\,sys}$ or $M_{D\,dias}/\sigma_{MD\,dias}$.

Test sample A, male results were for systolic, $t = 1.819$, $P > .05$; for diastolic, $t = 1.247$, $P > .2$. Test sample B, female results were for systolic, $t = .180$, $P > .8$; for diastolic, $t = .717$, $P > .4$. These differences are not significant, hence for the remainder of this study the fact that *Thieme* or *Finkle* measured the individual's blood pressure will be disregarded.

6. Individuals in the actual Puerto Rican sample were obtained in the following places, the numbers and percentages being indicated. Males—Hospital Out-Patients 305 (16.0%), Health Centers 895 (47.0%), University of Puerto Rico Students 133 (7.0%), Prisoners 394 (20.7%), and Miscellaneous 176 (9.2%). Females—Hospital Out-Patients 307 (20.4%), Health Centers 1090 (72.4%), and University of Puerto Rico Students 108 (7.1%).

Due to the low nutritional intake level in the general Puerto Rican population Hospital Out-Patients, who were never from nutritional class 1, are probably no more "sick" than the average of the rest of the population which is not in nutritional class 1. A Health Center is where "healthy" individuals come for a brief examination to obtain a medical certificate for a labor permit. The largest part of the sample came from such centers. University of Puerto Rico students are on the average from the upper nutritional classes. Miscellaneous means individuals obtained from such places as the Borinquen air base or parents of school children summoned

for examination. The prison system in Puerto Rico is not a harsh one, if anything food intake is more regular and perhaps slightly better than for non-prisoners. In short, a definite attempt was made to obtain as "healthy" individuals as possible.

7. Due to the fact that the male sample is composed of non-prisoners and prisoners the blood pressure means of these two groups were compared. The results are as follows. For 1509 non-prisoners the mean systolic pressure was 116.03 ± .39, the diastolic 71.19 ± .29. For 394 prisoners the mean systolic pressure was 117.04 ± .74, the diastolic 70.01 ± .51. t values are for systolic 1.21, and for diastolic 1.13, namely the differences are not significant. Therefore in subsequent analysis of the male sample the latter will include both non-prisoners and prisoners.

8. In the blood pressure analysis of the male and female Puerto Rican sample use is made of a ponderal index to delineate weight groups, and a body build index to delineate body build types. Some explanation is necessary regarding these indices.

The ponderal index concept is taken from *Robinson* and *Brucer*[1] who have used this index extensively in their blood pressure studies. This index is obtained by dividing body weight by height. In this study, body weight was measured in pounds and height in centimeters. *Pearl*[2] in a devastating criticism of various body build indices in general use defends, however, the Wt Ht index on the grounds that such an index is capable of straight forward physical interpretation and is easy to compute. The author of the present study is well aware that weight is a *hybrid* dimension as *Krogman*[3] has pointed out. Nevertheless, even if one could analyse the effect of the various components of weight, such as skeleton, plasma and total blood volume, extracellular fluid, etc., on blood pressure—obviously this would necessitate an extremely large sample not to mention laborious measuring techniques that cannot easily be carried out in the field.

Males were weighed dressed in a shirt and trousers, females in a dress, both sexes without shoes. Subsequently the ponderal index was calculated for every Puerto Rican male and female. The male mean ponderal index was 0.79 with a standard deviation of 0.10.

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[1] *Robinson, S.C., M. Brucer,* and *J. Mass:* Hypertension and Obesity. J. Lab. clin. Med. *25*, 807, 1940.

[2] *Pearl, R.:* An Index of Body Build. Amer. J. phys. Anthrop. *26*, 315, 1940.

[3] *Krogman, W.M.:* Review of "The Biology of Human Starvation" by *A. Keys* et al. Amer. J. phys. Anthrop. *10*, 229, 1952.

The female mean ponderal index was 0.72 with a standard deviation of 0.13. For males the ponderal index standard range, or $\pm$ one standard deviation, is therefore 0.69–0.89, for females 0.59–0.85. The standard range was arbitrarily used to delineate those individuals who fell into a *medium-weight* category. Those individuals with a ponderal index below the standard range were assigned to a *light-weight* category, those above the standard range to a *heavy-weight* category. The distribution curve for the male ponderal index shows a positive skewness of 0.60, using the formula 3 (Mean—Median)/σ, but there is no bi- or multimodality. The female distribution curve shows a positive skewness of 0.46, with no bi- or multimodality.

Robinson and *Brucer*[1] have also pointed out that the ponderal index, which expresses body weight in relationship to height, should not be confused with a body build index which expresses robustness or the lack thereof, i.e.:—a person possessing an intermediate body build may be a light-weight or a heavy-weight. *Robinson* and *Brucer* favor the relationship Chest Circumference/Height to delineate body build types. *Pearl* favors a habitus index obtained from the formula 100 $\times$ Chest Girth (at expiration) plus Abdominal Girth/Height. *Rees*[2] on the basis of the factorial analysis of the intercorrelations of 20 measurements on a group of 200 soldiers, proposes a body build index obtained from the formula 100 $\times$ Height/(Transverse Chest Diameter $\times$ 6). Unfortunately chest circumference and diameter measurements were only obtained on the Puerto Rican males, hence the decision was made to use some other body build index, which could be calculated for both the Puerto Rican males and females.

The body build index selected was Height/$\sqrt[3]{\text{Weight}}$. *Sheldon* et al.[3] have made use of this index in somatotyping. The results obtained from using such an index should be interpreted with caution because the index suffers from the fallacy of trying to equate body weight and body volume, also *Rees* maintains that female body build cannot be measured by a simple ratio. With these reservations in mind the body build index calculations are as

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[1] *Robinson, S.C.*, and *M. Brucer:* Body Build and Hypertension. Arch. intern. Med. *66*, 393, 1940.

[2] *Rees, L.:* The Value of Anthropometric Indices in the Assessment of Body Build. J. ment. Sci. *95*, 171, 1949.

[3] *Sheldon, W.H., S.S. Stevens*, and *W.B. Tucker:* The Varieties of Human Physique. Harper and Brothers, New York 1940.

follows. The male mean body build index was 12.8, with a standard deviation of 0.4. The female mean body build index was 12.6, with a standard deviation of 0.7. For males the body build standard range is therefore 12.4–13.2, for females 11.9–13.3. Those individuals with a body build index below the standard range were assigned to a *linear* category, those within and above the standard range to an *intermediate* and *lateral* category. These terms are merely useful for the present study and should not be confused with the Sheldonian terms of ecto-, meso- and endomorphy. The distribution curve for the male body build index shows a negative skewness of 0.75, with no bi- or multimodality. The female distribution curve shows a negative skewness of 0.42, with no bi- or multimodality.

General analysis of Puerto Rican blood pressures

A. The Effect of Age on Blood Pressure

Table 7 shows the male and female mean systolic and diastolic pressures. At first sight it would be tempting to declare the results

Table 7. The effect of age on blood pressure

		Male			
		Systolic		Diastolic	
Age	No.	Mean ± S.E.	σ ± S.E.	Mean ± S.E.	σ ± S.E.
17–19	92	113.04 ± 1.38	13.24 ± .97	66.76 ± .95	9.20 ± .67
20–24	588	113.92 ± .56	13.60 ± .39	68.17 ± .43	10.64 ± .30
25–29	418	115.37 ± .65	13.48 ± .46	70.31 ± .53	10.88 ± .37
30–34	300	117.24 ± .83	14.41 ± .58	72.56 ± .56	9.83 ± .40
35–39	227	119.38 ± 1.13	17.04 ± .79	74.61 ± .84	12.70 ± .59
40–44	171	118.69 ± 1.26	16.53 ± .89	74.42 ± .85	11.23 ± .60
45–49	84	121.61 ± 2.38	21.89 ± 1.68	74.98 ± 1.51	13.91 ± 1.07
50–54	23	122.60 ± 4.44	21.30 ± 3.14	72.52 ± 2.09	10.04 ± 1.47
All Ages	1903	116.24 ± .34	15.20 ± .24	70.94 ± .25	11.35 ± .18
		Female			
17–19	71	109.61 ± 1.18	9.98 ± .83	65.63 ± 1.07	9.06 ± .76
20–24	452	108.14 ± .56	11.96 ± .39	64.78 ± .43	9.31 ± .30
25–29	315	109.18 ± .82	14.69 ± .58	66.44 ± .58	10.30 ± .41
30–34	239	112.61 ± 1.16	18.04 ± .82	69.51 ± .77	11.97 ± .54
35–39	251	116.79 ± 1.12	17.87 ± .79	71.61 ± .71	11.35 ± .50
40–44	103	122.80 ± 2.83	28.79 ± 2.00	73.82 ± 1.30	13.26 ± .92
45–49	57	129.28 ± 3.16	23.89 ± 2.23	77.14 ± 1.61	12.18 ± 1.14
50–54	17	135.00 ± 6.88	28.37 ± 4.86	77.88 ± 3.64	15.03 ± 2.57
All Ages	1505	112.69 ± .46	17.88 ± .32	68.29 ± .29	11.39 ± .20

indicate that, in the case of the males, and particularly in regard to the females, blood pressure increases with increase in age. One should beware of such an easy temptation, into which so many analysers of human blood pressure have fallen. This can be illustrated in the following manner.

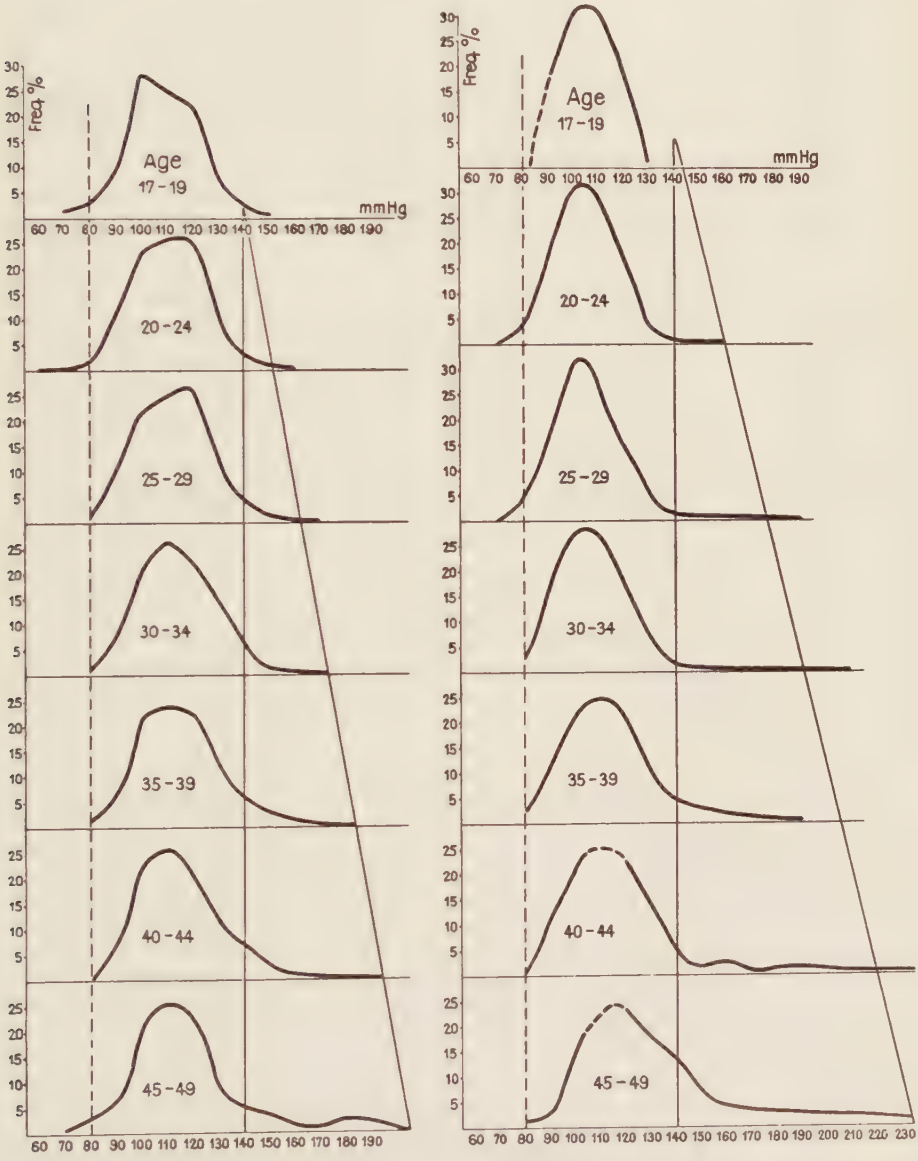

Fig. 2. Systolic Pressure.

Table 8. 140 systolic pressure and over in relationship to weight groups

	A No. in Wt. Groups			B No. in Wt. Groups with 140 Systolic and over			C 140 Systolic and over expressed as % of Wt. Groups			D % 140 Systolic and over of Wt. Groups All Wts
	Lt-Wt	Med-Wt	Hy-Wt	Lt-Wt	Med-Wt	Hy-Wt	Lt-Wt	Med-Wt	Hy-Wt	
Male										
17–19	13	72	7	–	2	1	—	2.8	14.3	3.3
20–24	87	449	52	–	16	4	—	3.6	7.7	3.4
25–29	50	307	61	–	15	5	—	4.9	8.2	4.8
30–34	31	218	51	2	14	5	6.5	6.4	9.8	7.0
35–39	26	165	36	2	23	4	7.7	13.9	11.1	12.8
40–44	20	118	33	1	13	6	5.0	11.0	18.2	11.7
45–49	16	56	12	2	6	5	12.5	10.7	41.7	15.7
50–54	4	16	3	1	4	–	25.0	25.0	—	21.7
Female										
17–19	1	65	5	–	–	–	—	—	—	—
20–24	59	366	27	–	2	1	—	0.5	3.7	0.7
25–29	31	249	35	1	8	2	3.2	3.2	5.7	3.5
30–34	23	166	50	–	10	3	—	6.0	6.0	5.4
35–39	28	173	50	2	15	10	7.1	8.7	20.0	10.8
40–44	8	78	17	–	12	4	—	15.4	23.5	15.5
45–49	4	33	20	1	10	6	25.0	30.3	30.0	29.8
50–54	1	11	5	–	4	2	—	36.4	40.0	35.3

Figure 2 shows the systolic pressure, by age groups, male and female, in the form of graphs where the percentage frequency is plotted against pressure. If one selects 140 mm Hg as an *arbitrary point* above which systolic pressure may be regarded as being "high", then the graphs show that with increase in age there is a gradual increase of individuals with a systolic pressure above 140 mm Hg, particularly in the case of the females.

An analysis, by age groups, of those individuals with 140 mm Hg and over systolic pressure reveals an interesting fact. Column D of Table 8 indicates that the percentage 140 and over systolic pressure of *all* weight groups increases with age, which is what the graphs show. However, column C indicates quite clearly that with increasing age the percentage particularly of *heavy-weights* with 140 and over systolic pressure increases, especially in the case of the females, and this fact clearly influences systolic pressure means.

Column C also seems to indicate that age may play some role in higher pressures in the light- and medium-weight groups, although it is perhaps most marked at the older ages.

It would appear then that the effect of age on blood pressure is not a simple one. In any event it would be wise, nay mandatory, to analyse the effect of weight groups on blood pressure in each age group.

B. The Effect of Weight Groups on Blood Pressure by Age

The Puerto Rican male and female samples were sorted into age groups and the latter into weight groups. The mean systolic and diastolic pressures of these were determined and are shown in Table 9.

Upon examination Table 9 indicates two salient points. First, in any age group, male or female, whether it be systolic or diastolic pressure, where sample numbers are adequate, the mean pressures are lowest in the light-weights, intermediate in the medium-weights and highest in the heavy-weights. This should be sufficient evidence to show the fallacy of giving mean pressures by age group without regard for weight group. However, one must remember the importance of variation. For example, in the male or female 35–39 age group, if one considers the range of systolic or diastolic pressure, it is evident that some light-weights have fairly high pressures and conversely some heavy-weights have somewhat low pressures. Naturally this point is always obscured in studies which only show mean pressures without the range or standard deviation.

Table 9. The effect of weight groups on blood pressure by age

Age	No.	Mean ± S.E.	σ ± S.E.	C.V.	Range
Light-Weight					
		Male Systolic			
17–19	13	102.46 ± 2.31	8.36 ± 1.63	8.15	88–122
20–24	87	111.21 ± 1.37	12.86 ± .97	11.56	68–134
25–29	50	111.66 ± 1.59	11.27 ± 1.12	10.09	86–138
30–34	31	112.25 ± 2.83	15.77 ± 2.00	14.04	88–150
35–39	26	109.80 ± 2.74	13.98 ± 1.93	12.73	88–148
40–44	20	110.60 ± 3.61	16.16 ± 2.55	14.61	90–152
45–49	16	115.00 ± 5.52	22.11 ± 3.90	19.22	72–180
50–54	4	129.00 ± 12.25	24.51 ± 8.66	19.00	106–170
		Male Diastolic			
17–19	13	60.76 ± 2.50	9.02 ± 1.76	14.84	46– 74
20–24	87	68.03 ± 1.18	11.04 ± .83	16.22	38– 98
25–29	50	66.72 ± 1.37	9.73 ± .97	14.58	50– 96
30–34	31	67.51 ± 1.65	9.22 ± 1.17	13.65	52– 90
35–39	26	67.23 ± 1.89	9.67 ± 1.34	14.38	44– 92
40–44	20	70.00 ± 2.44	10.91 ± 1.72	15.58	56– 98
45–49	16	68.25 ± 2.60	10.41 ± 1.84	15.25	40– 88
50–54	4	72.00 ± 3.39	6.78 ± 2.39	9.41	68– 82
		Female Systolic			
17–19	1	114.00	—	—	—
20–24	59	102.50 ± 1.32	10.21 ± .93	9.96	82–126
25–29	31	105.61 ± 2.85	15.88 ± 2.01	15.03	78–158
30–34	23	103.82 ± 1.89	9.10 ± 1.34	8.76	86–122
35–39	28	113.64 ± 2.63	13.93 ± 1.86	12.25	94–142
40–44	8	111.75 ± 6.20	17.56 ± 4.38	15.71	90–138
45–49	4	120.00 ± 11.02	22.04 ± 7.79	18.36	88–150
50–54	1	132.00	—		—
		Female Diastolic			
17–19	1	58.00	—	—	—
20–24	59	61.37 ± .98	7.56 ± .69	12.31	42– 78
25–29	31	63.80 ± 1.48	8.27 ± 1.05	12.96	48– 82
30–34	23	62.86 ± 1.76	8.44 ± 1.24	13.42	48– 80
35–39	28	70.35 ± 1.80	9.55 ± 1.27	13.57	50– 88
40–44	8	68.75 ± 2.97	8.42 ± 2.10	12.24	58– 82
45–49	4	68.00 ± 3.60	7.21 ± 2.54	10.60	58– 78
50–54	1	74.00	—	—	—

Table 9. The effect of weight groups on blood pressure by age (cont.)

Medium-Weight

Age	No.	Mean ± S.E.	σ ± S.E.	C.V.	Range
		Male Systolic			
17–19	72	113.38 ± 1.48	12.64 ± 1.05	11.14	78–150
20–24	449	113.60 ± .64	13.64 ± .45	12.00	74–160
25–29	307	114.98 ± .78	13.79 ± .55	11.99	82–170
30–34	218	116.71 ± .93	13.86 ± .66	11.87	80–160
35–39	165	119.96 ± 1.33	17.21 ± .94	14.34	84–182
40–44	118	119.20 ± 1.56	17.00 ± 1.10	14.26	86–194
45–49	56	119.28 ± 2.31	17.33 ± 1.63	14.52	94–184
50–54	16	123.25 ± 5.36	21.46 ± 3.79	17.41	94–160
		Male Diastolic			
17–19	72	67.27 ± 1.05	8.92 ± .74	13.25	46– 86
20–24	449	67.69 ± .50	10.63 ± .35	15.70	40–102
25–29	307	69.75 ± .61	10.72 ± .43	15.36	44–102
30–34	218	72.32 ± .67	9.89 ± .47	13.67	42–102
35–39	165	74.84 ± 1.00	12.89 ± .70	17.22	48–122
40–44	118	73.61 ± 1.03	11.24 ± .73	15.26	48–112
45–49	56	73.58 ± 1.42	10.69 ± 1.00	14.52	50–112
50–54	16	72.75 ± 2.86	11.44 ± 2.02	15.72	58– 92
		Female Systolic			
17–19	65	109.92 ± 1.26	10.16 ± .89	9.24	90–136
20–24	366	108.60 ± .60	11.60 ± .42	10.68	74–142
25–29	249	108.55 ± .90	14.35 ± .64	13.21	82–190
30–34	166	112.31 ± 1.42	18.35 ± 1.00	16.33	80–210
35–39	173	115.09 ± 1.24	16.35 ± .87	14.20	80–190
40–44	78	121.91 ± 3.38	29.92 ± 2.39	24.54	84–278
45–49	33	130.78 ± 4.41	25.34 ± 3.11	19.37	100–232
50–54	11	136.63 ± 10.16	33.70 ± 7.18	24.66	100–200
		Female Diastolic			
17–19	65	66.06 ± 1.13	9.17 ± .80	13.88	44– 88
20–24	366	65.04 ± .48	9.21 ± .34	14.16	40– 98
25–29	249	66.06 ± .64	10.21 ± .45	15.45	42–112
30–34	166	69.40 ± .97	12.60 ± .69	18.15	40–120
35–39	173	70.54 ± .85	11.22 ± .60	15.90	44–108
40–44	78	72.75 ± 1.45	12.85 ± 1.02	17.66	50–120
45–49	33	77.63 ± 2.31	13.32 ± 1.63	17.15	58–128
50–54	11	80.90 ± 5.08	16.84 ± 3.59	20.81	64–114

Table 9. The effect of weight groups on blood pressure by age (cont.)

Heavy-Weight

Age	No.	Mean ± S.E.	σ ± S.E.	C.V.	Range
		Male Systolic			
17–19	7	129.14 ± 3.29	8.71 ± 2.32	6.74	114–144
20–24	52	121.26 ± 1.59	11.47 ± 1.12	9.45	94–155
25–29	61	120.36 ± 1.57	12.27 ± 1.11	10.19	96–152
30–34	51	122.52 ± 2.02	14.45 ± 1.43	11.79	100–170
35–39	36	123.66 ± 2.58	15.53 ± 1.83	12.55	102–174
40–44	33	121.75 ± 2.33	13.41 ± 1.65	11.01	104–150
45–49	12	141.33 ± 8.26	28.64 ± 5.84	20.25	102–200
50–54	3	110.66 ± 1.60	2.77 ± 1.13	2.50	108–114
		Male Diastolic			
17–19	7	72.57 ± 2.70	7.16 ± 1.91	9.86	60– 82
20–24	52	72.53 ± 1.26	9.10 ± .89	12.54	44– 92
25–29	61	76.04 ± 1.37	10.73 ± .97	14.11	50–112
30–34	51	76.62 ± 1.18	8.45 ± .83	11.02	60– 99
35–39	36	78.88 ± 1.90	11.43 ± 1.34	14.49	64–116
40–44	33	80.03 ± 1.54	8.87 ± 1.09	11.08	64– 99
45–49	12	90.50 ± 5.50	19.08 ± 3.89	21.08	62–136
50–54	3	72.00 ± 1.88	3.26 ± 1.33	4.52	68– 76
		Female Systolic			
17–19	5	104.80 ± 2.16	4.83 ± 1.52	4.60	98–112
20–24	27	114.29 ± 2.84	14.78 ± 2.01	12.93	90–164
25–29	35	116.88 ± 2.19	12.99 ± 1.55	11.11	90–156
30–34	50	117.68 ± 2.57	18.23 ± 1.82	15.49	94–190
35–39	50	124.44 ± 3.14	22.26 ± 2.22	17.88	88–178
40–44	17	132.11 ± 6.02	24.83 ± 4.25	18.79	102–194
45–49	20	128.65 ± 4.75	21.25 ± 3.35	16.51	92–178
50–54	5	132.00 ± 6.71	15.01 ± 4.74	11.37	120–158
		Female Diastolic			
17–19	5	61.60 ± 2.73	6.11 ± 1.93	9.91	54– 72
20–24	27	68.74 ± 2.19	11.41 ± 1.55	16.59	44– 94
25–29	35	71.48 ± 1.85	10.96 ± 1.30	15.33	50– 99
30–34	50	72.94 ± 1.36	9.63 ± .96	13.20	56–110
35–39	50	76.02 ± 1.64	11.62 ± 1.16	15.28	52–102
40–44	17	81.11 ± 3.47	14.31 ± 2.45	17.64	60–112
45–49	20	78.15 ± 2.26	10.14 ± 1.60	12.97	60–101
50–54	5	72.00 ± 4.19	9.38 ± 2.96	13.02	62– 86

Second, Table 9 gives one some clue to the effect of age on blood pressure in the weight group in question. In this case it would be best to confine oneself to the age groups 20–24 to 45–49, because of the sample numbers involved.

In regard to the *light-weight* group it is extremely interesting to note that for systolic or diastolic pressure, male or female, there is no significant difference in pressures between the age groups 20–24 and 45–49. Male t values are for systolic 0.66, for diastolic 0.07. Female t values are for systolic 1.57, for diastolic 1.77.

The *medium-weight* group presents a somewhat conflicting picture. Between the age groups 20–24 and 45–49 the male systolic pressure shows no significant difference, t value 2.37, but the male diastolic pressure shows a significant difference between the age groups 20–24 and 25–29, t value 2.64, and thereafter to the age group 45–49. Between the age groups 20–24 and 30–34 the female systolic pressure shows no significant difference, t value 2.43, but after age 35 the difference is significant. The female diastolic pressure shows no significant difference between the age groups 20–24 and 25–29, t value 1.29, but after age 30 the difference is significant.

The *heavy-weight* group results are as follows. Between the age groups 20–24 and 45–49 the male systolic pressure shows no significant difference, t value 2.39. The male diastolic pressure shows no significant difference between the age groups 20–24 and 30–34, t value 2.37, but after age 35 the difference is significant. Between the age groups 20–24 and 35–39 the female systolic pressure shows no significant difference, t value 2.39, but after age 40 the difference is significant. The female diastolic pressure shows no significant difference between the age groups 20–24 and 30–34, t value 1.63, but after age 35 the difference is significant.

In the heavy-weight group, in later years, more individuals have higher systolic pressures, particularly females, as has been already seen in Table 8, indicating that *the duration of obesity is an important factor in the establishment of higher pressures.*

Calculation of the median systolic pressure gives the following results, with the mean values shown in parenthesis. Light-weight group, age 20–24, male 112.4 (111.2), female 102.3 (102.5); age 45–49, male 115.5 (115.0), female 114.5 (120.0). Medium-weight group, age 20–24, male 113.9 (113.6), female 109.3 (108.6); age 45–49, male 117.1 (119.2), female 130.2 (130.7). Heavy-weight group,

age 20–24, male 121.8 (121.2), female 113.3 (114.2); age 45–49, male 134.5 (141.3), female 127.5 (128.6).

This comparison of the median and mean values indicates that the greater increase of the mean compared to the median, between the ages of 20– and 49, is due to the high readings of a comparatively small number of individuals and not to the general group of males or females. Therefore in any weight group in this sample, ages 20–49, male or female, it is doubtful that one could make the unequivocal statement that blood pressure increases with age.

Various investigators of human blood pressure have suggested that the diastolic pressure measurement is a more accurate indicator of possible ill-health, because they felt, based doubtless on the standard deviation, that the systolic varied more than the diastolic pressure. Again Table 9 indicates that in all weight groups the male or female systolic pressure, by age group, has a larger absolute variation (standard deviation) than the diastolic pressure. But if one considers the relative variation (coefficient of variation), then up to 45 years of age say, for male or female, the diastolic varies more than the systolic pressure, except that in the female heavy-weight group the relative variation of the diastolic is greater than that of the systolic pressure only up to age 30.

Is there an absolute and/or relative increase in the range of readings with age? Apparently this depends on whether you are considering systolic or diastolic pressure. In all weight groups the trend seems to be, for male or female, that there is both an absolute and relative increase in age for the systolic but not the diastolic pressure.

Is the range of systolic and diastolic pressure, both absolutely and relatively, greater for females or males at ages over 40? In the light-weight group it is in general greater for males. In the medium-weight group it is greater for females, and in the heavy-weight group greater for females except in the age group 45–49. These results should be interpreted cautiously because small numbers are involved in the age groups over 40.

As an indicator of ill-health therefore, from the *statistical* point of view, it is somewhat debatable as to which is the "best" blood pressure measurement to use—the systolic or diastolic.

It is not the purpose of this study to explain the etiology of obesity, but to point out its effect on blood pressure. It is interesting to note that the relationship between weight and blood pressure

was noticed as long ago as 1922 by *Symonds*[1], using insurance company records for males. Arranging his study by build groups on a weight per unit height basis, he observed an increase in pressure with an increase in relative obesity for all ages. Using a small sample of white male and female cardiacs, compared to non-cardiacs, *Pearl* and *Ciocco*[2] and *Ciocco*[3] have shown that the cardiacs were characterized as a group by greater body weight. *Schwartz*[4] with a private patient male and female sample, and *Robinson* and *Brucer*[5] with an insurance company sample of both sexes, have proved that at any age group light-weights have lower pressures than heavy-weights.

Short and *Johnson*[6] using insurees of unspecified sex, have pointed out that with an increase in overweight there is a marked decrease in vital capacity, furthermore that when overweight persists long enough to produce postural changes the vital capacity remains impaired regardless of weight reduction. *Dublin* and *Marks*[7] using insurance company data for females, have shown that the trend of mortality, over 30 years of age, is a progression from low mortality for under-weights to high mortality among the obese. *Wilens*[8] using 1250 necropsies, male and female results mixed, has indicated that within any decade, over 35 years of age, the incidence of severe atherosclerosis is from 2 to 4 times greater in the obese than in the "poorly nourished", the latter presumably being the non-obese or light-weights. Finally *Hahn*[9], using an English school-

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[1] *Symonds, B.:* Blood Pressure of Healthy Men and Women. J. Amer. med. Ass. *80*, 232, 1922.

[2] *Pearl, R.,* and *A. Ciocco:* Studies on Constitution; II. Somatological Differences associated with Diseases of the Heart in White Males. Hum. Biol. *6*, 650, 1934.

[3] *Ciocco, A.:* Studies on Constitution. II. Somatological Differences associated with Diseases of the Heart in White Females. Hum. Biol. *8*, 38, 1936.

[4] *Schwartz, J.:* Clinical Study of Blood Pressure in relation to Body Weight. Med. Rec. *152*, 102, 128, 1940.

[5] *Robinson, S.C., M. Brucer,* and *J. Mass:* Hypertension and Obesity. J. Lab. clin. Med. *25*, 807, 1940.

[6] *Short, J.J.,* and *H.J. Johnson:* The Effect of Overweight on Vital Capacity. Proc. Life Ext. Examin. *1*, 36, 1939.

[7] *Dublin, L.I.,* and *H.H. Marks:* The Build of Women and its relation to their Mortality. Proc. Ass. Life Insur. med. Dir. Amer. *25*, 203, 1939.

[8] *Wilens, L.L.:* Bearing of General Nutritional State on Atherosclerosis. Arch. intern. Med. *79*, 129, 1947.

[9] *Hahn, L.:* The Relation of Blood Pressure to Weight, Height and Body Surface Area in Schoolboys Aged 11 to 15 Years. Arch. Dis. Childh. *27*, 43, 1952.

boy sample, ages 11–15, points out that theoretically at any of these ages one would expect a lower pressure in light-weights and a higher pressure in heavy-weights.

It is unnecessary to continue this recitation of evidence. Some authors still maintain that there is no relationship between weight or weight groups and blood pressure. It is no longer necessary to attempt to prove the relationship—it is already obvious, and the Puerto Rican sample which is far more representative of the general population than any of the above samples, is an excellent added piece of evidence.

C. The Concept of Normal Blood Pressure

There has been for many years some confusion in the medical literature regarding the difference between average and normal blood pressure. As *Stanley* and *Alvarez* stated in 1930[1], "It should be obvious that if one decides to accept for insurance only those persons whose blood pressures fall within the limits of, let us say, 100 to 140 mm Hg, the average is bound to come out at about 120 mm."

Since most blood pressure standards of normality in the U.S.A. have been based on insurance company samples, such standards are clearly suspect for they reflect biased averages. In addition, most of the earlier studies quoted averages without mentioning either the standard error or standard deviation of the mean. In other words, the fact that blood pressure varies like any other biological phenomenon was ignored. Many medical practitioners in their private practice frequently have patients with a blood pressure 25–50 mm above the "average", nevertheless these patients continue to live a full life span. Therefore as *Bordley* and *Eichna*[2] have pointed out, "—the limits of normal blood pressure as applied to groups by insurance companies are far too narrow to be applied to individuals."

The resounding fallacy that underlies the above confusion is that the sampling technique of almost every investigator, from the point of view of establishing blood pressure norms, has been incredibly bad. Indubitably no blood pressure sample yet exists that

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[1] *Alvarez, W.C.*, and *L.L. Stanley:* Blood Pressures in 6000 Prisoners and 400 Prison Guards. Arch. intern. Med. *46*, 17, 1930.

[2] *Bordley, J.*, and *L.W. Eichna:* Normal Blood Pressure. Int. Clin. *1*, 175, 1938.

is representative of the general population of the U.S.A., and one can hardly use the excuse that the available census material is inadequate. Insurance company samples represent a highly selected group of "accepted risks". *Robinson* and *Brucer*[1], after criticizing this very point, proceeded to attempt to establish the range of normal blood pressure by using an insurance company sample of individuals who lived in and around Chicago, were mostly urban, relatively sedentary, and earned $ 1000 or over per annum! Some samples purporting to show the influence of age on blood pressure in the aged, such as *Master* et al.[2], were obtained almost entirely in New York City or, such as *Russek*[3], from the "Sailors Snug Harbor", presumably also in New York City.

A more recent and ambitious attempt to obtain a representative sample of the general population was done by *Master* et al.[4]. Even here the sample is taken from only 9 states and represents civilian workers in industrial plants and army airfields. These examples are typical of supposedly "representative" samples. I shall resist the temptation of continuing this dreary list.

On the other hand, if one does obtain a representative sample of a given population, then blood pressure means with their standard deviations at least give one a basis from which one can proceed to establish the range of normal blood pressure as it applies to the given population. However, since weight groups obviously affect blood pressure, within any age group, the range of normal blood pressure should be stated in terms of the weight groups, and not just by age groups in which the weight groups are lumped together. This is another common error.

Treloar[5] has stated that, "It is well recognised in biostatistics that any attempt to fix limits of normal variation in a physiologic function is extremely hazardous." Nevertheless some arbitrary limits of normal blood pressure are necessary if one is trying to define statistically the range of normal blood pressure and also for

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[1] *Robinson, S.C.*, and *M. Brucer:* The Range of Normal Blood Pressure. Arch. intern. Med. *64*, 409, 1939.

[2] *Master, A.M., H.H. Marks*, and *S. Dack:* Hypertension in People over 40. J. Amer. med. Ass. *121*, 1251, 1943.

[3] *Russek, H.I.:* Blood Pressure in the Aged. A Study of 1000 Elderly Male Subjects. Amer. Heart J. *26*, 11, 1943.

[4] *Master, A.M., L.I. Dublin*, and *H.H. Marks:* The Normal Blood Pressure Range and its Clinical Implications. J. Amer. med. Ass. *143*, 1464, 1950.

[5] *Treloar, A.E.:* Normal Blood Pressure. Arch. intern. Med. *66*, 848, 1940.

comparative purposes. The arbitrary limits should not produce a sharp dividing line between normal and abnormal pressures, for this situation does not exist in real life.

Regarding this matter *Master* et al.[1] state that, "Certainly we may assume that any reading within one standard deviation of the mean is probably within the normal range, and it is not unreasonable to extend this normal range to cover 80 per cent of the observations, that is, 40 per cent on either side of the mean. On the other hand, any blood pressure reading departing $2\,\sigma$ or more from the mean is probably abnormal." This approach does not ignore the fact that blood pressure varies and the arbitrary limits of normal and abnormal pressures are probably consistent with the average general practitioner's experience.

A similar approach to the range of normal blood pressure is followed in this study. This is illustrated in Table 10, which should be of considerable use to the general practitioner in Puerto Rico. In this table, "normal" refers to pressures $1.28\,\sigma$ or 40 per cent on either side of the mean, "lower" and "upper" refer to a pressure $1.96\,\sigma$ on either side of the mean. In this Puerto Rican sample, then, according to weight and age group, those pressures below the lower limit and those above the upper limit are probably abnormal. The zones lower-normal and normal-upper represent possibly borderline hypo- and hypertensive cases.

Table 10 also indicates, especially in the light-weight group, that the lower limit of normal diastolic pressure in Puerto Rico is around 55 mm Hg. This does not necessarily mean that the individual is suffering from fatigue or lessened vitality. Light-weights tend to have low blood pressures.

As *Robinson*[2] has stated, "—it is clear that low blood pressure does not cause fatigue or lessened vitality, any more than high blood pressure causes an increase in physical efficiency. The degree of health or mental and physical fitness is not an attribute of blood pressure levels; rather it depends upon cellular oxidation and biochemical changes and these, in turn, aside from hereditary differences, are to a great degree dependent upon the extent of daily work an individual performs." Perhaps it would be better to say that mental and physical fitness depend in general upon a satis-

[1] *Master* et al., op. cit.

[2] *Robinson, S.C.:* Hypotension: The Ideal Normal Blood Pressure. New Engl. J. Med. *223*, 407, 1940.

Table 10. The range of normal blood pressure by age and weight groups

Age	Lt-Wt			Med-Wt			Hy-Wt		
	Lower	Normal	Upper	Lower	Normal	Upper	Lower	Normal	Upper
				Male Systolic					
20–24	86	95–128	136	87	96–131	140	99	107–136	144
25–29	90	97–126	134	88	97–133	142	96	105–136	144
30–34	81	92–132	143	90	99–134	144	94	104–141	151
35–39	82	92–128	137	86	98–142	154	93	104–144	154
40–44	79	90–131	142	86	97–141	153	95	105–139	148
45–49	82*	87–143	148*	85	97–141	153	98*	105–178	184*
				Male Diastolic					
20–24	46	54–82	90	47	54–81	89	55	61–84	90
25–29	48	54–79	86	49	56–83	91	55	62–90	97
30–34	49	56–79	86	53	60–85	92	60	66–87	93
35–39	48	55–80	86	50	58–91	100	56	64–94	101
40–44	49	56–84	91	52	59–88	96	63	69–91	97
45–49	48	55–82	89	53	60–87	95	64*	66–115	118*
				Female Systolic					
20–24	82	89–116	123	86	94–123	131	85	95–133	143
25–29	74	85–126	137	80	90–127	137	91	100–134	142
30–34	86	92–115	122	76	89–136	148	82	94–141	153
35–39	86	96–131	141	83	94–136	147	81	96–153	168
40–44	77	89–134	146	80*	84–160	181	83	100–164	181
45–49	77	92–148	163	81	98–163	180	87	101–156	170
				Female Diastolic					
20–24	47	52–71	76	47	53–77	83	46	54–83	91
25–29	48	53–74	80	46	53–79	86	50	57–86	93
30–34	46	52–74	79	45	53–86	94	54	61–85	92
35–39	52	58–83	89	49	56–85	93	53	61–91	99
40–44	52	58–80	85	48	56–89	98	53	63–99	109
45–49	54	59–77	82	52	61–95	104	58	65–91	98

To find proper weight group, divide weight in pounds, by height in inches multiplied by 2.54 cms. Weight group ponderal index ranges are as follows:—MALE. Lt-Wt X—0.68. Med-Wt 0.69—0.89. Hy-Wt 0.90—X. FEMALE. Lt-Wt X—0.58. Med-Wt 0.59—0.85. Hy-Wt 0.86—X.

* Estimated.

factory state of nutrition and that the latter determines to a large extent the work capabilities of an individual.

D. The Effect of Body Build on Blood Pressure

The Puerto Rican males and females were sorted into the three categories of linear, intermediate and lateral body build. These, in turn, were sorted into light-, medium- and heavy-weight groups. This technique of course disregards age.

The reason for using the above technique is that *Robinson*[1] has pointed out that weight should be separated from build in order to see the relative effect of each on blood pressure. Using an insurance company male and female sample, *Robinson* claimed that when the weight factor is held constant, no matter what the weight group, for both male and female mean systolic and diastolic pressures increase from the linear to lateral build type.

In Table 11, the results marked (a) show that for Puerto Rican males, within any weight group, as one proceeds from linear to lateral build mean systolic and diastolic pressures increase somewhat. However, none of these differences is significant. If one compares the weight groups, within the same build groups, the differences between means are significant. For example, linear build—light- to medium-weight systolic t value is 4.17, diastolic 4.31. Intermediate build—light- to heavy-weight systolic t value is 4.28, diastolic 3.88. Lateral build—medium- to heavy-weight, systolic t value is not significant, but the diastolic t value is 3.99.

Now it must be remembered that in this study body build was obtained by using the formula Height $\sqrt[3]{\text{Weight}}$. *Robinson* and *Brucer*[2] have maintained that the formula Chest Circumference/Height is a better delineator of body build. As has been mentioned before the chest circumference measurement was taken only on the Puerto Rican males. Accordingly the formula Chest Circumference/Height was used to delineate body build for the Puerto Rican males. The mean of the latter formula was 0.52 with a standard deviation of 0.03, giving a standard range of 0.49 to 0.55, to which the intermediate build corresponds. Below 0.49 are linears and above 0.55 laterals. The mean systolic and diastolic pressures based

[1] *Robinson, S.C.:* Hypertension, Body Build and Obesity. Amer. J. med. Sci. *199*, 819, 1940.

[2] *Robinson, S.C.*, and *M. Brucer:* Body Build and Hypertension. Arch. intern. Med. *66*, 393, 1940.

Table 11. Body build and weight groups in relation to blood pressure

			Male		
			Lt-Wt	Med-Wt	Hy-Wt
Linear	No	(a)	163	226	—
		(b)	113	164	—
	Systolic Mean ± S.E.	(a)	111.04 ± 1.04	116.88 ± .94	—
		(b)	111.31 ± 1.37	115.59 ± 1.16	—
	Diastolic Mean ± S.E.	(a)	67.72 ± .75	72.34 ± .77	—
		(b)	66.88 ± .97	70.96 ± .92	—
Inter-mediate	No.	(a)	84	1058	53
		(b)	133	1134	109
	Systolic Mean ± S.E.	(a)	111.83 ± 1.81	115.37 ± .45	122.49 ± 1.72
		(b)	112.69 ± 1.33	116.33 ± .44	123.03 ± 1.22
	Diastolic Mean ± S.E.	(a)	66.98 ± 1.27	69.83 ± .33	74.01 ± 1.30
		(b)	68.63 ± .94	70.74 ± .33	75.50 ± .84
Lateral	No.	(a)	—	117	202
		(b)	1	103	146
	Systolic Mean ± S.E.	(a)	—	119.18 ± 1.46	122.80 ± 1.09
		(b)	—	120.90 ± 1.67	123.95 ± 1.39
	Diastolic Mean ± S.E.	(a)	—	72.70 ± .97	77.65 ± .79
		(b)	—	74.30 ± 1.01	79.15 ± .98

(a) Based on Body Build Formula Height/$\sqrt[3]{\text{Weight}}$.
(b) Based on Body Build Formula Chest Circumference/Height.

on the formula Chest Circumference/Height are marked (b) in Table 11.

The latter results show a trend very similar to the results obtained by using the formula Height/$\sqrt[3]{\text{Weight}}$. Holding body weight constant, only the heavy-weight—intermediate to lateral build diastolic pressure difference is definitely significant, with a t value of 2.85. On the other hand holding build constant, in each weight group from lighter to heavier weight, either the systolic or diastolic pressure differences are significant.

The female results are shown in Table 12. Within any weight group as one proceeds from linear to lateral build the mean systolic and diastolic pressures increase, but with the exception of light-weight—linear to intermediate build mean diastolic pressure difference, t value 2.63—none of the differences is significant. In the linear build—light- to medium-weight, the mean systolic difference

Table 12. Body build and weight groups in relation to blood pressure

		Female		
		Lt-Wt	Med-Wt	Hy-Wt
Linear	No.	99	64	—
	Systolic Mean ± S.E.	104.44 ± 1.30	109.60 ± 1.72	—
	Diastolic Mean ± S.E.	62.88 ± .84	67.89 ± 1.18	—
Inter-mediate	No.	56	1042	48
	Systolic Mean ± S.E.	110.21 ± 1.94	112.13 ± .54	115.72 ± 2.71
	Diastolic Mean ± S.E.	66.83 ± 1.26	67.81 ± .35	70.08 ± 1.81
Lateral	No.	—	35	161
	Systolic Mean ± S.E.	—	112.77 ± 2.90	122.55 ± 1.56
	Diastolic Mean ± S.E.	—	68.34 ± 2.13	74.85 ± .88

is not significant, but the diastolic is significant, t value 3.47. In the intermediate build—light- to heavy-weight, neither the mean systolic nor diastolic difference is significant. In the lateral build—medium- to heavy-weight, the mean systolic difference is significant, t value 2.97, also the diastolic, t value 2.83.

As far as the females are concerned a trend similar to the males is observable although not so clear cut. This is probably due to the fact that the correlation between body build and ponderal indices is greater in the males, i.e.:—male r = –.917, female r = –.730. It is possible that the formula Chest Circumference Height, if it be the correct formula to use on females, might give results more in favor of body build than body weight.

The Puerto Rican sample, therefore, indicates that weight groups in males definitely, and in females probably, exert a greater effect on blood pressure than build groups.

E. The Effect of Urban or Rural Life on Blood Pressure

There is a rather widespread idea that hypertension and urbanization are correlated. For example, *Donnison*[1] states, "The literary evidence available affords quite an adequate amount of information regarding the incidence of hyperpiesis, ...its incidence increases with development of towns and with education...". He gives no actual methodological proof for this statement.

[1] *Donnison, C. P.:* Civilization and Disease. Wood, Baltimore 1938.

Hashimoto et al.[1], using a sample of 3530 males and 6528 females, both sexes being poor out-patients who attended St. Luke's International Hospital in Tokyo, claimed a percentage of hypertension slightly over 9.0, hypertension being defined as a persistent systolic pressure of over 160 and diastolic over 100 mm Hg. As the authors point out the high incidence of hypertension in a hospital sample may be due to the hospital having a well-known cardiovascular clinic. In addition the authors state that the incidence of hypertension is higher among Japanese than Chinese. They evidently compared their sample with a sample of Chinese from the Hunan-Yale Hospital in S. China. The Chinese were presumably rural, and since both Japanese and Chinese are mongoloid, then the difference in the incidence of hypertension must be due not to race but to urbanization. An ingenious explanation based on no methodological proof whatsoever.

On the other hand *Gover*[2], using a low-income farm (rural) sample of 2749 males and 2582 females drawn from only 17 states in the U.S.A., came to the conclusion that the mean systolic pressure of specific age groups was *higher* than that of industrial urban workers, the mean diastolic pressure being about the same. This author's urban workers are mainly drawn from Insurance Company samples, whose representativeness of urban workers throughout the U.S.A. is to be seriously questioned. Furthermore, weight groups in the rural and urban samples were not equated. Again the methodological approach is valueless.

Using the Puerto Rican sample the following methodology was used to test the possible difference between urban and rural life on blood pressure.

Obviously the first desideratum is that the individual should have lived all his or her life in an urban or rural area. Incidently this important point is by no means clear in those blood pressure studies which have endeavored to test the effect of urban or rural life. Therefore all those "all life" urban or rural *non-prison* males and urban or rural females were first sorted out in the Puerto Rican sample.

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[1] *Hashimoto, H., K. Akatsuka, I. Tsujii,* and *H. Shiraishi:* The Incidence of Hypertension among Urban Japanese. Ann. intern. Med. 7, 615, 1933/4.

[2] *Gover, M.:* Physical Impairments of Members of Low-Income Farm Families. VII. Variation of Blood Pressure and Heart Disease with Age; and the Correlation of Blood Pressure with Height and Weight. Publ. Hlth. Rep. *63*, 1083, 1948.

Random samples of 150 urban non-prison males and 200 urban females were then obtained and analyzed in regard to the following variables:—age groups 20–44, weight group, nutritional class and ethnic group. For example, age group 20–24 and subsequent age groups were divided into light-, medium- and heavy-weight groups, and each weight group analyzed regarding the number in each ethnic group who fell into nutritional classes 1–4. By random sorting rural non-prison male and rural female samples were obtained equal in number to the urban sample, each individual in the rural sample being matched with a similar individual in the urban sample. Finally both urban and rural samples were compared to the Puerto Rican calculated sample concerning the region distribution, prior to the actual test for significance of difference of blood pressure.

Table 15. The effect of urban or rural life on blood pressure

	Male		Female	
	Urban	Rural	Urban	Rural
No.	150	150	200	200
Av Age	27.0	27.6	27.2	27.3
% Lt-Wt	14.4	14.4	12.0	12.0
% Med-Wt	73.9	73.9	78.5	78.5
% Hy-Wt	11.7	11.7	9.5	9.5
Av Ht^2/Wt	12.84 ± .04	12.87 ± .04	12.72 ± .04	12.68 ± .04

%		A	B	C	D	A	B	C	D
Region	1.	5.0	3.3	5.0	6.0	3.5	3.5	9.0	7.1
	2.	25.0	56.0	45.0	23.0	24.5	51.4	30.0	24.4
	3.	2.2	3.0	3.0	8.7	5.5	3.5	7.0	8.5
	4.	22.2	20.5	11.1	19.0	28.0	19.9	15.5	18.8
	5.	15.3	19.0	10.0	10.2	14.0	10.7	8.5	10.4
	6.	6.1	3.3	6.7	11.5	8.5	3.2	14.0	11.4
	7.	25.0	8.1	10.0	14.8	16.0	7.8	16.0	19.5

A and C. Actual Urban and Rural.
B and D. Calculated Urban and Rural.

Systolic				
Mean ± S.E.	116.75 ± 1.01	115.92 ± 1.17	111.50 ± 1.05	112.07 ± 1.05
Diastolic				
Mean ± S.E.	71.20 ± .79	71.31 ± .87	69.75 ± .71	67.90 ± .66
Systolic				
Range	90–150	76–154	84–146	82–152
Diastolic				
Range	44–110	44–118	42–110	44–108

The results are shown in Table 13 and are self-explanatory with the exception of the region distribution and the mean systolic and diastolic pressures. The percentage region distribution figure is the per cent of the total regions, urban or rural. The main discrepancy is in region 2, but this is merely a reflection of the region urban-rural distribution of the actual Puerto Rican sample to be seen in Table 5. The mean systolic and diastolic pressures with their accompanying standard errors are indicated purely as a matter of interest in this and subsequent tables dealing with matched samples. The test for significance of difference is *not* conducted using these standard errors, because we are dealing here again with matched samples or samples whose means are correlated.

Applying then the correct test for significance of difference between matched samples, as was done in the *Thieme-Finkle* test samples, the results are as follows:—Male urban-rural systolic pressure, $t = .564$, $P > .5$, diastolic $t = .108$, $P > .9$. Female urban-rural systolic pressure, $t = .795$, $P > .4$, diastolic $t = 1.526$, $P > .1$. None of these differences is significant.

Hence it would appear that Puerto Ricans living in urban areas do not have higher blood pressures than those in rural areas, or the reverse.

F. The Effect of Nutritional Class on Blood Pressure

Information regarding the nutritional aspect of Puerto Ricans was obtained mainly from the study of the main aspects of family living in Puerto Rican families of all socio-economic levels carried out by *Lydia Roberts*, *Rosa Stefani* and their co-workers[1]. This study used a representative sample of 1044 families and was done in 1946. The validity of this sample—determined by checking against the 1940 U.S. Census, concerning such variables as urban-rural distribution, age distribution, size of family, sex distribution and home ownership—is of noteworthy soundness.

Unfortunately all results concerning the adequacy of Puerto Rican diets in this study are given in percentages. The standards used for comparison were the recommended dietary allowances of the Food and Nutrition Board, National Research Council, Washington, D.C. Any dietary standard possesses the properties of a mean and the latter should be accompanied by its standard error and

[1] *Roberts, L. J.*, and *R. L. Stefani:* Patterns of Living in Puerto Rican Families. Dept. of Home Economics, University of Puerto Rico 1949.

standard deviation for comparative purposes, as has been pointed out by *Dann* and *Darby*[1]. In any nutritional survey of a population the dietary intake results should be expressed in a similar fashion, as was done for example in a Tennessee rural population nutritional survey by *Youmans* et al.[2].

Nevertheless *Roberts* and *Stefani*'s Puerto Rican dietary study is the best we have so far. The authors have pointed out that Puerto Rican diets may be classed roughly into four main types.

In type I, comprising 12.8 per cent of all families the day's diet, at its poorest, is made up almost entirely of *viandas* (starchy vegetables or fruits), rice, or *some other starchy food.* This diet is very low in all dietary factors, with the possible exception of calories. The intake of protein is only 50 per cent of the recommended daily allowance. Calcium and all the B vitamins meet only one fourth of the allowances, and vitamins A and C even less. This diet, at its best, with some codfish and a little milk, is markedly deficient in good protein, calcium and vitamin A.

In type II, comparising 33.6 percent of all families, the day's diet is made up mostly of *rice and beans.* A diet of this type, at its poorest, fails to meet even 75 per cent of the daily allowances in everything but calories, protein and iron. Such a diet is extremely low in vitamins A and C, and at its best it is around 75 per cent of the allowances or less in all dietary factors, in fact below 25 per cent in calcium and vitamin A. Types I and II are typical of families with incomes less than $ 500 per year.

In type III, comprising 47.1 per cent of all families, the day's diet is made up mostly of *rice, beans and viandas.* This diet is better than the preceding ones especially in thiamine and iron. At its poorest, the diet is very low in calcium, vitamins A and C and riboflavin. At its best, with some codfish or other protein and milk it is still low in the above dietary factors. Type III is typical of families with incomes of $ 500 to $ 1999 per year. The general inadequacy of type I–III diets is well-nigh incredible.

In type IV, comprising 6.5 per cent of all families, diets are

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[1] *Dann, W.J.*, and *W.J. Darby:* The Appraisal of Nutritional Status (Nutriture) in Humans. With Especial Reference to Vitamin Deficiency Diseases. Physiol. Rev. *25*, 326, 1945.

[2] *Youmans, J.B., E.W. Patton* and *R. Kern:* Surveys of the Nutrition of Populations. Description of the Population, General Methods and Procedures, and the Findings in respect to the Energy Principle (Calories) in a Rural Population in Middle Tennessee. Part. 2. Amer. J. Publ. Hlth. *33*, 58, 1943.

in general adequate and are typical of families with an income of $ 2000 and over per year. In this category diets contain meat or other protein food at two meals, soup once or twice, and one pint of milk or more per person daily. They also contain a good share of lard and sugar but the amounts of vegetables and fruits vary considerably. Interestingly enough upper income families also like to eat a portion of rice and beans. In fact, during my sojourn in Puerto Rico, my landlord—an upper income family man—informed me that when he was visiting New York City, what he missed most in American restaurants was his "rice and beans". Type IV diets are adequate in all dietary factors with the possible exception of vitamins A and C, depending upon the intake of vegetables and fruits.

For the purposes of the present study types IV, III, II and I were called nutritional classes 1, 2, 3 and 4. Since the above diets differ, especially nutritional class 1, any possible effect of this diet difference on blood pressure ought to be examined. Of course in the present case it is only possible to test the effect on blood pressure of one *type* of diet versus another. One is not testing here *one* dietary factor, the others being held constant. The latter kind of study on a representative sample of a given population, to my knowledge, has yet to be done.

It is worth mentioning at this point regarding the relationship of diet and hypertension that *Chapman* and *Gibbons*[1], in an excellent and exhaustive criticism, citing 226 references, of past and present experiments performed almost entirely on hospital patients, have concluded that none of the following has a definitely provable therapeutic value in hypertension:—low intake of the sodium or chloride ion, including the so-called famous *Kempner* rice diet, which limits the intake of protein, salt, fluids and possibly calories; low intake of fat and cholesterol; excess or lack of protein, caffeine, alcohol, guanidine base compounds, watermelon seed or garlic (!). In fact the only positive conclusion the authors arrive at concerns caloric intake, i.e.:—obesity is associated with an increased incidence of hypertension and weight loss in obese hypertensive patients often results in a decline in the blood pressure levels.

In spite of *Chapman* and *Gibbons*' conclusions the possible effect of the different nutritional classes in Puerto Rico on blood

[1] *Chapman, C. B.*, and *T. B. Gibbons:* The Diet and Hypertension. Medicine, Baltimore. 29, 29, 1950.

pressure was tested using the following methodology, omitting nutritional class 4 since unfortunately too few males and females belonging to this class existed in the actual Puerto Rican sample.

Since there may be a dietary difference between prisoners and non-prisoners in Puerto Rico only non-prison males were used. Also since only 100 males and 102 females belonging to nutritional class 1 existed in the actual Puerto Rican sample the resultant samples for the test were not large. Random samples of 85 urban or rural non-prison males and 95 urban or rural females belonging to nutritional class 1 were obtained and analysed in regard to the following variables:—age groups 17–49, weight group, region and ethnic group. For example, age group 17–19 and subsequent age groups were divided into light-, medium- and heavy-weight groups, and each weight group analysed regarding the number in each region who fell into ethnic groups 0–8. By random sorting male and female nutritional class 2 and 3 samples were obtained equal in number to the nutritional class 1 sample, each individual in the nutritional class 2 and 3 samples being matched with a similar individual in the nutritional class 1 sample.

The results are shown in Table 14. Applying the correct test for significance of difference between matched samples the results are as follows:—Male—nutritional class 1 and 2 systolic pressure, $t = .092$, $P > .9$, diastolic $t = 1.831$, $P > .05$. Nutritional class 1 and 3 systolic pressure, $t = 1.175$, $P > .2$, diastolic $t = 1.814$, $P > .05$. Nutritional class 2 and 3 systolic pressure, $t = .889$, $P > .3$, diastolic $t = .110$, $P > .9$. Female—nutritional class 1 and 2 systolic pressure, $t = .157$, $P > .8$, diastolic $t = .330$, $P > .7$. Nutritional class 1 and 3 systolic pressure, $t = .806$, $P > .4$, diastolic $t = .922$, $P > .3$. Nutritional class 2 and 3 systolic pressure, $t = .666$, $P > .5$, diastolic $t = .571$, $P > .5$. None of these differences is significant.

Therefore as far as nutritional classes 1–3 in Puerto Rico are concerned nutritional class *per se* does not appear to exert an influence on blood pressure.

However, attention is drawn to the bottom of Table 14 where each nutritional class is analysed concerning the percentage proportion of the weight groups. This shows quite clearly that the quantity and quality of the diet affects the proportion of weight groups, i.e.:—nutritional class 1, male or female, has a much larger proportion of heavy-weights than light-weights. Nutritional class 1 is also made up of families in the upper income bracket. In other words in Puerto Rico, the higher the income the better the quantity

Table 14. The effect of nutritional class on blood pressure

	Male			Female		
	N.C. 1	N.C. 2	N.C. 3	N.C. 1	N.C. 2	N.C. 3
No.	85	85	85	95	95	95
Av Age	27.9	26.6	27.2	28.0	28.3	27.9
% Lt-Wt	3.5	3.5	3.5	4.2	4.2	4.2
% Med-Wt	67.1	67.1	67.1	67.4	67.4	67.4
% Hy-Wt	29.4	29.4	29.4	28.4	28.4	28.4
Av $Ht/\sqrt[3]{Wt}$	12.69	12.70	12.58	12.41	12.48	12.42
	± .06	± .06	± .06	± .07	± .07	± .07
Systolic						
Mean ± S.E.	116.41	116.23	114.73	110.00	110.38	111.74
	±1.32	±1.69	±1.86	±1.48	±2.03	±1.63
Diastolic						
Mean ± S.E.	71.88	68.95	69.91	66.65	67.08	67.84
	± .97	±1.28	±1.32	± .90	±1.20	±1.16
Systolic						
Range	92–158	82–162	76–164	80–178	80–190	82–172
Diastolic						
Range	56–102	42–118	42–102	48– 95	44–104	46–102
	Lt-Wt %	Med-Wt %	Hy-Wt %	Lt-Wt %	Med-Wt %	Hy-Wt %
N. C. 1	3.0	57.0	40.0	3.9	62.7	33.3
N. C. 2	12.3	75.2	12.5	10.2	76.7	13.2
N. C. 3	16.9	72.5	10.6	12.4	77.1	10.5
N. C. 4	29.7	67.6	2.7	17.1	77.1	5.7

and quality of the diet and hence the more chance of putting on weight, especially since individuals belonging to this nutritional class occupationally probably are mostly sedentary workers. And yet as we have already seen the greater the amount of obesity the greater is the tendency for higher blood pressure levels.

If, as was done, the nutritional classes are *equated* in regard to the afore-mentioned variables, particularly weight groups, no significant difference is observable regarding the effect of the different nutritional classes on blood pressures. This suggests that the type of diet is not directly related to blood pressure levels but only indirectly insofar as nutritional class 1 has the greatest proportion of heavy-weights.

G. The Effect of Climatic Environment on Blood Pressure

Most of the existing studies on the relationship between climate and blood pressure have dealt with the effect of a temperate or tropical climate. The consensus of opinion is that "hypotension" exists in the tropics. The word "hypotension" is ill-chosen because it almost always has the connotation of a blood pressure that is below "normal" and hence "abnormal". By this criterion all lightweights in Puerto Rico have "abnormal" blood pressures, which is absurd.

Various reasons have been advanced in order to explain this so-called "hypotension", such as:—a lowered peripheral resistance associated with increased secretory activity of the sweat glands; dilation of peripheral blood vessels, as well as increased elasticity of the vessel wall; the comparatively slower and calmer life in the tropics; a decreased capacity for muscular effort with a resulting decrease in muscular tone; diet; and on the rare occasion that a smaller stature and lighter weight might be important factors. All of these suggestions, however, are based on results exhibiting extremely poor methodology, and as long as the latter continues they will be entirely speculative.

Examples of the poor methodology used are: *Scott* et al.[1], who subjected individuals to warm or cool rooms and observed the results on blood pressure, or *Miller* and *Moor*[2], who put 113 syphilitic (!) patients in a fever cabinet—neither of these experiments represent acclimatization; or *Roddis* and *Cooper*[3], *Radsma* et al.[4] or *MacPherson*[5], who used one group of individuals in a temperate and another in a tropical climate, ignoring such important variables as age, weight groups or diet.

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[1] *Scott, J.C., H.C. Bazett* and *G.C. Mackie:* Climatic Effects on Cardiac Output and the Circulation in Man. Amer. J. Physiol. *129*, 102, 1940.

[2] *Miller, V.J.*, and *F.B. Moor:* Acute Effects of Hot Saturated Atmosphere upon the Human Temperature, Heart Rate, and Blood Pressure, as influenced by Age. Brit. J. phys. Med. *10*, 167, 1947.

[3] *Roddis, L.H.*, and *G.W. Cooper:* The Effect of Climate on Blood Pressure. J. Amer. med. Ass. *87*, 2053, 1926.

[4] *Radsma, W., J.T. Meijman* and *G.G.A. Mastenbroek:* Measurements of Pressure and Pulse Frequency of White Men in the Tropics and Colder Climates. Ned. Tijdschr. Geneesk. *82*, 4679, 1938.

[5] *MacPherson, R.K.:* The Effect of Exposure to Humid Tropical Climates on the Resting Pulse Rate and Arterial Blood Pressures. Fatigue Lab. Nat. Hlth. and Med. Res. Counc., Australia, Open Report No. 7, 1, 1946.

Exactly the same criticism can be leveled at those studies concerning the relationship between altitude and blood pressure, i.e.:— *Smith*[1], *Latham*[2] or *Allegretti*[3]. Incidently aviation altitude is not acclimatization either.

As far as Puerto Rico is concerned the possible effect of climate on blood pressure is of course not one of a temperate versus a tropical climate. Nor does Puerto Rico have any area of great altitude. However, it does possess two regions, namely 6 and 7, both of which are mountainous and at the same time humid, and a southern lowland region, namely 4, which is also arid. It is of some interest to test the possible difference of these climatological regions on blood pressure.

The two climatological regions then to be tested are regions 6 and 7 taken together, omitting Caguas from the latter which is a valley, and region 4. In a test involving the effect of climate it must be obvious that the individual should have lived all his or her life in the same region, in fact in the same municipio. Naturally this reduces the *number* of individuals or *regions* available for a test sample. Accordingly such individuals were first sorted out. For males this meant using only non-prison males. For the purposes of the test the following methodology was used.

Random samples of 73 "all life" non-prison urban or rural males and 100 "all life" urban or rural females belonging to region 4 were obtained and analysed in regard to the following variables:— age groups 20–49, weight group, nutritional class and ethnic group. For example, age group 20–24 and subsequent age groups were divided into light-, medium-, and heavy-weight groups, and each weight group analysed regarding the number in each nutritional class that fell into ethnic groups 0–8. By random sorting male and female region 6 plus 7 samples were obtained equal in number to the region 4 samples, each individual in the former samples being matched with a similar individual in the latter samples.

The results are shown in Table 15. Applying the correct test for significance of difference between matched samples the results are as follows:—Male region 4 versus region 6 plus 7 systolic pres-

[1] *Smith, F.C.:* The Effect of Altitude on Blood Pressure. J. Amer. med. Ass. *64*, 1812, 1915.

[2] *Latham, D.V.:* The White Man in East Africa. East Afr. med. J. *9*, 276, 1932/3.

[3] *Allegretti, A.J.:* Blood Pressure as affected by Altitude. Med. Bull. vet. Admin. *19*, 290, 1943.

Table 15. The effect of climatic environment on blood pressure

	Male		Female	
	Region 4	Region 6+7	Region 4	Region 6+7
	(Arid)	(Humid)	(Arid)	(Humid)
No.	73	73	100	100
Av Age	29.6	29.8	29.1	28.9
% Lt-Wt	15.1	15.1	8.0	8.0
% Med-Wt	76.7	76.7	78.0	78.0
% Hy-Wt	8.2	8.2	14.0	14.0
Av $Ht/\sqrt[3]{Wt}$	12.93 ± .06	12.86 ± .49	12.61 ± .70	12.61 ± .77
Systolic Mean ± S.E.	116.14 ± 1.61	116.00 ± 1.47	113.30 ± 1.96	117.40 ± 1.70
Diastolic Mean ± S.E.	69.56 ± 1.14	71.07 ± 1.23	67.30 ± 1.04	71.00 ± 1.21
Systolic Range	72–146	90–144	82–190	82–188
Diastolic Range	42– 94	40– 94	40– 96	42–120

sure, $t = .221$, $P > .8$, diastolic $t = .955$, $P > .3$. Female region 4 versus region 6 plus 7 systolic pressure, $t = 1.720$, $P > .05$, diastolic $t = 2.371$, $P > .01$. By the criterion of the 1 per cent level of confidence none of these differences is significant.

Therefore it would appear that in Puerto Rico the climate of the different regions in question does not seem to influence blood pressure.

However, in view of the fact that the climatic differentiation of the regions is perhaps not marked, the above conclusion should be treated as a tentative one.

H. The Effect of Intestinal Parasites on Blood Pressure

It has been known for a long time that the incidence of intestinal infestation is very high in Puerto Rico. *Otero* and *Perez*[1], using a sample of 8898 adult male rural agricultural workers, ages 20 to 65 and over, drawn mainly from 48 municipios, have shown that, taking the sample as a whole, 75.8 per cent of all workers had some

[1] *Otero, Morales P.*, and *M.A. Perez:* Health and Socio-Economic Studies in Puerto Rico. IV. Physical Impairments of Adult Life among Agricultural Workers. Puerto Rico J. publ. Hlth. trop. Med. *15*, 285, 1940.

kind of intestinal parasitic infestation. The percentage breakdown of the latter is as follows:—Uncinaria (hookworm) 91.2, Ascaris 12.1, Trichuris 48.3, Schistosoma 0.2, and Other Intestinal Parasites 0.1.

Weller and *Dammin*[1], used a sample of 19,139 male Puerto Rican Selective Service registrants, ages 18 38, who were mostly urban and from all municipios, but in what proportion compared to the 1940 Census we are not told. For the total group the incidence of intestinal parasitic infestation was 88.3 per cent. Of those with positive parasites the percentage breakdown is as follows:—Hookworm 64.0, Ascaris 7.6, Trichuris 86.4, Schistoma 11.2, Strongyloides Stercoralis 11.7, and Other Intestinal Parasites 0.1.

In view of the fact that the first sample is composed of male rural agricultural workers and the second sample is mainly urban, consisting of "relatively healthy and well-educated adult males with proportionately few laborers from the sugar, tobacco, and coffee-farming areas"—the difference between the samples in the percentage incidence of hookworm, trichuris and schistoma is not without interest.

There is a fairly prevalent belief in medical circles that there is a correlation between "low" blood pressure and the infestation of parasites, particularly ascaris or hookworm[2]. This belief is not shared by all as can be seen in the case of *Saunders*[3] and *Torgerson*[4]. Because of these conflicting views it was considered to be worthwhile to test the possible difference between those with and those without intestinal parasitic infestation on blood pressure.

Concerning this point it is worth noting that, regarding intestinal parasites in 1947 I stated[5], "One wonders again what could be the effect of such infestation on blood pressure—The time has come to cease wondering. A study on blood pressure should be done, in an area having intestinal parasites, using one group known to be free of the parasites as control, and another group that does have them."

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[1] *Weller, T.H.*, and *G.J. Dammin:* The Incidence and Distribution of Schistoma Mansoni and Other Helminths in Puerto Rico. Puerto Rico J. publ. Hlth. trop. Med. *21*, 125, 1945.

[2] *Heilig, R.:* The Pathological Heart Conditions in Hookworm Disease and their Causes. Indian med. Gaz. *77*, 257, 1942.

[3] *Saunders, G.M.:* Blood Pressure in Yucatecans. Amer. J. med. Sci. *185*, 843, 1933.

[4] *Torgerson, W.R.:* Blood Pressure Findings in Puerto Rico. Puerto Rico J. publ. Hlth. trop. Med. *5*, 438, 1930.

[5] *Murrill*, op. cit.

Fecal examinations were done only on part of the total Puerto Rican sample because we were not asked to collect fecal specimens until some time after we had started to collect the main sample, also many individuals who said they would return with a specimen did not do so.

From 1509 non-prison males results were obtained on only 501 individuals or 33.2 per cent. 70.5 per cent of the 501 individuals were positive and 29.5 per cent were negative in parasites. From 1505 females results were obtained on only 603 individuals or 40.1 per cent. 63.8 per cent of the 603 individuals were positive and 36.2 per cent were negative in parasites.

The following methodology was used to obtain the test samples. Random samples of 125 non-prison urban or rural males and 125 urban or rural females who were negative in parasites were first obtained and analysed in regard to the following variables:—age groups 20–44, weight group, nutritional class and ethnic group. For example, age group 20–24 and subsequent age groups were divided into light-, medium- und heavy-weight groups, and each weight group analysed regarding the number in each nutritional class that fell into ethnic groups 0–8. By random sorting male and female positive parasite samples were obtained equal in number to the negative parasite samples, each individual in the former samples being matched with a similar individual in the latter samples.

As far as these positive parasite samples are concerned they represent individuals with any kind of intestinal parasitic infestation, whether single or mixed.

The results are shown in Table 16. Applying the correct test for significance of difference between matched samples the results are as follows:—Male parasites, positive versus negative systolic pressure, $t = 1.558$, $P > .1$, diastolic $t = 1.419$, $P > .1$. Female parasites, positive versus negative systolic pressure, $t = .489$, $P > .6$, diastolic $t = .163$, $P > .8$. None of these differences is significant.

Considering the fact that fecal examinations were performed only on a portion of the total Puerto Rican sample, the percentage region distribution of the positive and negative parasite samples, shown in Table 16, when compared with the calculated region distribution is encouraging. The main discrepancies are in the male positive parasite sample region 2, and in the female positive parasite sample regions 2 and 6. Caution then is indicated in interpreting the results of the test samples.

Table 16. The effect of intestinal parasites on blood pressure

	Male			Female		
	Positive		Negative	Positive		Negative
No.	125		125	125		125
Av Age	30.8		31.5	30.9		31.0
% Lt-Wt	21.6		21.6	11.2		11.2
% Med-Wt	68.8		68.8	76.0		76.0
% Hy-Wt	9.6		9.6	12.8		12.8
Av Ht/$\sqrt[3]{\text{Wt}}$	$12.85 \pm .05$		$12.90 \pm .05$	$12.50 \pm .05$		$12.57 \pm .06$
%	A	B	C	A	B	C
Region 1.	5.5	7.2	3.2	5.6	7.2	4.8
2.	34.5	24.0	38.4	35.1	16.0	35.2
3.	6.7	6.4	3.2	6.5	5.6	4.8
4.	19.6	12.8	18.4	19.2	16.0	20.8
5.	10.3	11.2	3.2	10.5	16.8	4.8
6.	8.3	13.6	12.0	8.2	22.4	11.2
7.	15.1	24.8	21.6	14.9	16.0	18.4
Systolic Mean $\pm$ S.E.	115.75 ± 1.22		118.68 ± 1.36	116.28 ± 1.77		115.84 ± 1.75
Diastolic Mean $\pm$ S.E.	$71.39 \pm .92$		73.25 ± 1.04	69.84 ± 1.04		70.08 ± 1.09
Systolic Range	82–152		90–176	80–220		84–194
Diastolic Range	50– 98		50–122	44–110		48–112

A. Calculated Region Distribution. B. Actual Positive Parasite Distribution. C. Actual Negative Parasite Distribution.

Nevertheless the results of the test samples show that in all probability, whether an individual has an intestinal parasitic infestation or not in Puerto Rico, this has no appreciable effect on blood pressure.

I. Summary and Conclusions regarding the Most Important Variables affecting Blood Pressure in Puerto Rico

As far as this general analysis of Puerto Rican blood pressure is concerned the evidence indicates that the most important variables affecting blood pressure are weight groups and possibly age in relation to weight groups.

It has been shown also that in Puerto Rico the following variables exert no appreciable effect on blood pressure:—body build, urban or rural life, nutritional class, climate of the two regional areas tested, and intestinal parasitic infestation.

It might be argued by some that the effect of urban or rural life, etc., on blood pressure should have been tested first before coming to any conclusions regarding, say, "normal" blood pressure in Puerto Rico. On the contrary, the effect of the different weight groups on blood pressure is outstanding and this had to be demonstrated first and then incorporated into the various test samples.

It should now be apparent that if one is going to compare two populations regarding any possible blood pressure differences that certain basic precautions are essential. First, the samples must be as representative as possible of the populations in question. Second, weight groups are important, for example, if one sample has a great preponderance of heavy-weights and the other does not, the former will probably have higher mean systolic and diastolic pressures. Third, although the evidence in Puerto Rico shows that certain variables such as urban or rural life, etc., have no appreciable effect on blood pressure, until additional similar evidence is forthcoming from other areas in the world one cannot as yet ignore these variables, particularly in the case of racial blood pressure studies.

Summary

This study is not concerned specifically with hypertension, arteriosclerosis or arteriolosclerosis.

It is concerned with the methodology involved in discerning the most important variables affecting blood pressure, based on a representative male and female Puerto Rican sample. This study indicates the range of normal blood pressure of the 1948 Puerto Rican population, particularly ages 20–49, with due regard of such variables as sex, age, weight groups, etc. It also shows that the most important variables affecting blood pressure are weight groups and possibly age in relation to weight groups, and that the following variables exert no appreciable effect on blood pressure:—body build, urban or rural life, nutritional class, the climate of two main Puerto Rican regions, and intestinal parasitic infestation.

Résumé

Ce travail ne concerne pas particulièrement l'hypertension, l'artériosclérose ou l'artériolosclérose, mais s'occupe de la méthode de recherche des principales variables qui influencent la tension artérielle, en prenant pour base un matériel représentatif d'habitants des deux sexes de Porto-Rico. L'auteur indique les variations de la pression sanguine normale de la population de Porto-Rico en 1948, en particulier chez des sujets âgés de 20 à 49 ans, compte tenu de l'influence du sexe, de l'âge, du poids, etc. Il ressort de cette étude que les variables les plus importantes affectant la tension artérielle sont le poids et, éventuellement, l'âge par rapport au poids. En revanche, les variables suivantes n'exercent pas d'effet appréciable sur la tension artérielle: la constitution, la vie urbaine ou rurale, la nutrition, le climat des deux régions porto-ricaines principales, ainsi que la parasitose intestinale.

Zusammenfassung

Diese Untersuchung befaßt sich nicht speziell mit Hypertension, Arteriosklerose oder Arteriolosklerose, sondern mit der Methodik der Erkenntnis der wichtigsten Variablen, die den Blutdruck beeinflussen. Als Material diente eine Gruppe von männlichen und weiblichen Einwohnern von Puerto Rico. Der Autor gibt die normalen Blutdruckwerte an, wie sie 1948 bei 20- bis 49jährigen Bewohnern von Puerto Rico festgestellt wurden, wobei Variable wie Geschlecht, Alter, Gewicht usw. berücksichtigt wurden. Als wichtigste den Blutdruck beeinflussende Variable bezeichnet er das Gewicht und möglicherweise das auf das Gewicht bezogene Alter, während Körperbau, Stadt- oder Landleben, Ernährung, das Klima in zwei bedeutenden Regionen Puerto Ricos, sowie Darmparasitosen keine nennenswerte Rolle spielen.

Bibliographic Note

I consider that those references marked with an asterisk have contributed most to this study in the bibliography which follows.

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Author's address:
Dr. R. J. Murill, Dept. of Sociology and Anthropology University of Kansas, *Lawrence*, Kan. (U. S. A.)

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ON THE CONCEPTS AND CALCULUS OF PENETRANCE

By CARL-GUSTAF BERGLIN, Göteborg

1. Concepts of penetrance

In genetics, the general concept of penetrance has several meanings. It may denote the frequency with which a gene produces any effect at all [1], the "manifestation force" of a gene. Or it may refer to the probability that a characteristic phenotype will appear in a certain genotype [2]. Mathematically, the two concepts often belong to very different orders of magnitude. One and the same phenotype may correspond to a 5 per cent penetrance of a gene and to a 60 per cent penetrance of a genotype. A third concept refers to the percentage of trait-carriers amongst gene-carriers [11].

Dahlberg stresses the importance of prenatal environment and random variation in the cytoplasm of the different cells [3] for the manifestation of some phenotypes but he also calls attention to the necessary hereditary basis for such markedly constellational traits [4] and concludes that the vague concept of penetrance may be said to express the probability that a gene under varying environmental circumstances and in varying combinations with other genes will participate in the manifestation of a certain phenotype [5].

The problem thus, at first sight, is a very complex one. Discarding for the moment the question of variation in environmental factors, we yet have to consider several kinds of gene factor combinations, such as polyallelia, polyhybridia, and inversion [6], further different types of homozygotes and of heterozygotes. It is therefore indispensable, whenever we discuss penetrance problems, to define as clearly as possible the pertinent environmental factors as well as the gene factors with which we are dealing in each separate case.

This task may previously have appeared as one of mainly academic interest. The situation has changed radically since *Trankell* published his quantitative theory of penetrance in 1954 [7], initiated

by his studies of left-handedness [8] (although the theory is independent of the genetic questions concerning that phenotype). The present author, in collaboration with *Trankell*, has attempted to generalize the calculus of penetrance in some respects. As will be seen later, the calculus leads to some very definite concepts of penetrance, that must be defined here.

The penetrance of a gene may be defined as the part of all gametes, carrying this gene-factor, that participates in the manifestation of the phenotypic trait. Quantitatively, we may express it as the quotient of manifested gene-factors and all gene-factors of a certain kind within a population. For this quotient, the author proposes the term *genetrance* of the specific gene factor.

The penetrance of a zygote may be defined as the part of all zygotes of a certain type that participates in the manifestation of the phenotypic trait. For the quotient of the manifested zygotes and all zygotes of that specific kind, the author proposes the term *zygotrance* of such and such zygotes.

Those concepts are valid only under defined environmental circumstances, so that for instance a certain zygotrance may (and very often does) vary from stratum to stratum in the population, according to age. Genetrance varies according to both environmental and mating conditions. It is worth noticing that neither gene-carriers nor trait-carriers provide us immediately with the values we need for the quotients.

2. Some postulates in the penetrance calculus

Scientific methods may tell us whether a hypothesis is false or possibly true, but never whether it is true [9]. Parallel hypotheses may cover the situation equally well or better. This applies of course to the calculation of penetrance too, but in its generalized form the method has the advantage of offering a hierarchy of hypotheses so that several possibilities can be excluded under one and the same heading.

The calculus forms a branch of population genetics. It does not apply to probands and families. Counting all members contained in a representative sample of a total population stratum as well as their parents and, in some instances, their grandparents or children, *Trankell*'s penetrance calculus enables us to look into domains of genetics, hitherto inaccessible to quantitative analysis. It starts from, inter alia, the following facts and hypotheses.

In a defined population stratum we discern two phenotypes that mutually exclude each other. Suppose we call them A and $\overline{A}$. The relative size of all strata being 1, let the phenotypes have the proportions a and (1−a).

On the nonphenomenological level, we postulate two mutually excluding gene factors, D and R, having the proportions d and (1−d). For the sake of convenience [10], the symbol r is sometimes used instead of (1−d), and (1−r) instead of d. It is important to note that neither D nor R imply any assumption of dominance or recessivity, as far as the penetrance calculus is concerned. It is a characteristic feature of the theory in its generalized form that a phenomenon such as dominance is regarded only as a relatively uninteresting limit value. The gene-factors combine to three kinds of zygotes: DD, DR, and RR.

For the time being, the theory is confined to this general hypothesis of monohybridic diallelia. It presupposes that the individuals in regard to their sets of remaining gene-factors are distributed according to a pattern, constant from group to group within the stratum, although not constant from individual to individual. It also assumes that cytoplasmatic influences, as well as pertinent prenatal and postnatal influences from environmental factors, form the same characteristic pattern within each subgroup. The last-mentioned condition will of course seem very difficult to control, since unsuspected factors may disturb the picture. This topic has been discussed at considerable length, including from statistical points of view, since the birth of the theory. The discussion has convinced the author that environmental factor patterns that differ from subgroup to subgroup should reveal themselves by unbalancing the calculation. Differing environmental patterns that do not unbalance the calculus would either behave exactly like gene-factors, which seems a very unwarranted presumption or else form a very improbable combination of zygotrance quotients (see section 10).

It might be added that the theory of penetrance presupposes isofertility but not panmixis within the population. The strict formulae assume isofertility and panmixis within each subgroup. The corrected formulae make provision for deviations within the sample from such ideal conditions.

Very probably, the list of basic hypotheses given in this section will have to be further extended in the future. Sex differences and

other genetic influences have to be considered in some cases, for instance.

3. *Types of zygotrance in monohybridic diallelia*

The penetrance calculus takes into account that A may appear in each of the genotypes DD, DR, and RR. The zygotrance of a certain genotype is said to be 1 if every member shows the trait. If no member shows the trait, the zygotrance is said to be 0; this is equivalent to the zygotrance 1 for the opposite trait $\bar{A}$. If some members show A and some show $\bar{A}$, the zygotrance has some value between 1 and 0. Such values will in the following often be indicated by the symbol +.

Starting from three genotypes we may then arrive at 27 possible combinations. Let DD have the zygotrance 1, and DR the same value. RR may now have the values 1, –, or 0. Change the DR symbol to –, and three new possibilities arise, etc. In a recent paper [13], *Trankell* has pointed out, however, that the 27 cases are partly identical. If DD, DR, and RR have the values 0 0 1 respectively (corresponding to complete recessive zygotrance in RR), we could as well use the formulae (1 0 0), (1 1 0), or (0 1 1), since it is purely a matter of convention if we call the gene-factor D instead of R, or the trait $\bar{A}$ instead of A.

Table 1

	DD	DR	RR
I	1	1	1
II	1	0	0
III	1	0	1
IV	+	0	0
V	1	–	0
VI	0	–	0
VII	0	1	+
VIII	–	–	0
IX	–	1	+
X	+	–	+

In the light of similar considerations, the types of zygotrance boil down to a number of ten, listed in table 1. From the general case (+ + +) we may derive all the rest by letting each plus-sign vary from zero to one. The detailed algebraic formula of this case (see section 5) enables us to construct easily the modified formulae

of the other nine cases. The case (+ + 0) or, inversely, (+ + 1) comes next to it, as far as generality is concerned. It is of special interest since it leads to a definite solution (see section 6), based on material from three consecutive generations. Types with less than two plus signs require only two generations. The type (1 1 1) represents traits common to the species, e.g. "lack of tail" in man; its identical inversion (0 0 0) would read "tail-carrying" in man. The four types III, VI, VII and IX correspond to the queer-looking but in no way impossible situation that a trait is enhanced or, inversely, suppressed in the heterozygotes.

4. Quantities used in the penetrance calculus

In the following, the relative size of each population stratum (for instance a paternal generation, or all individuals of a certain age) is considered to be 1. All proportions of a stratum are written in small letters, e.g. a and (1–a). Fractions within a proportion (e.g. a zygotrance) are written as quotients or sometimes in capital letters. Capital letters are also given to absolute numbers and to some non-quantitative entities, such as phenotypes and gene-factors. The index 1, 2 or 3 indicates consecutive generations.

Phenotypical quantities. In three consecutive generations, numbering N_1, N_2 and N_3 individuals, we find A_1, A_2 and A_3 trait-carriers, respectively. The trait A, then, has the relative proportions $\frac{A_1}{N_1} = a$, $\frac{A_2}{N_2} = b$, and $\frac{A_3}{N_3} = a_3$. The alternative trait $\overline{A}$ has therefore the proportions (1–a) in the first, (1–b) in the second, and ($1-a_3$) in the third generation.

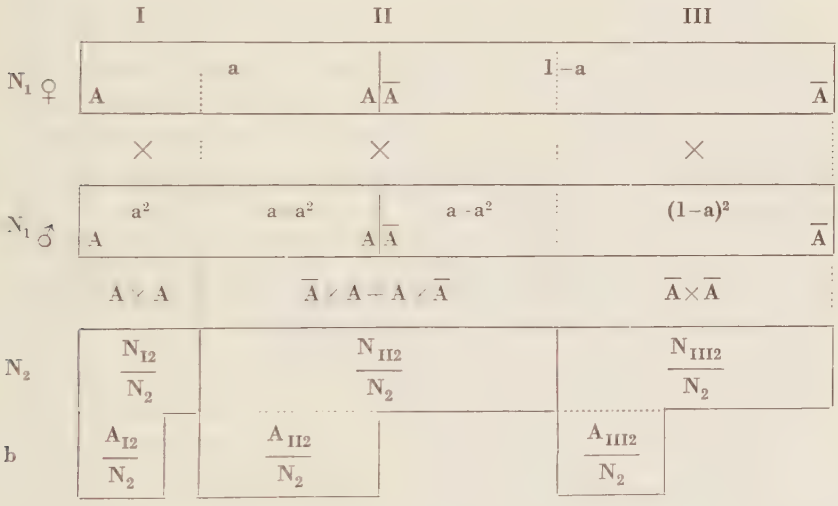
Within each generation, three types of matings occur, namely $A \times A$, $A \times \overline{A}$, and $\overline{A} \times \overline{A}$. The index I, II, or III indicates the mating type (the "family group"). The probability that we shall find an A is a, and the chance that this A shall have found another A is a^2. Thus the proportion of $A \times A$-parents in N_1 is a^2, and the proportion of their children in N_2 is a^2, too, as long as panmixis and isofertility prevails. Family group II has the proportion $2a(1-a)$, group III the proportion $(1-a)^2$.

Let $A \times A$ have N_{I2} children, $A \times \overline{A}$ have N_{II2} and $\overline{A} \times \overline{A}$ have N_{III2} children. Ideally, then, the N_2 members of the second generation form the children groups $\frac{N_{I2}}{N_2} = a^2$, $\frac{N_{II2}}{N_2} = 2a(1-a)$, and $\frac{N_{III2}}{N_2} = (1-a)^2$. Within these groups, the trait-carriers A_2 are

distributed with A_{I2} in the first, A_{II2} in the second, and A_{III2} in the third group, so that $\frac{A_{I2}}{N_2} + \frac{A_{II2}}{N_2} + \frac{A_{III2}}{N_2} = b$.

In some cases, it may prove necessary to proceed to the third generation in an analogous manner. The $A \diagdown A$-families this time have the proportion b^2, their N_{I3} children the same proportion b^2, the trait-carriers among those children the proportion $\frac{A_{I3}}{N_3}$, and so on.

Diagram 1 describes graphically the phenomenological aspect of a mating. The first row corresponds to a stratum of mothers, the second row to a stratum of fathers. Both rows are divided into one proportion of trait-carriers and one of non-trait-carriers. In the second row, subdivisions point to the proportions that will participate in the different kinds of matings. The third row gives the proportions of children, as well as the subproportions of trait-carriers. Each stratum is supposed to be of the relative size 1.



All quantities necessary for the calculation so far are directly observable. A somewhat queer feature of the technique is the fact that the exact determination of the trait A is indispensable only in the N_2- and N_3-generations. In the N_1-generation, it is enough to make sure that no $\bar{A}$-individuals go to the a-proportion, while it is of no consequence if the (1 - a)-proportion contains some individuals who have been mistaken for $\bar{A}$ though they rightly should belong to the trait-carriers, according to some formal definition.

Non-observable quantities. In all strata we tentatively postulate two gene-factors, D and R. Under the condition that no selection takes place, they always have the proportions d and $r = (1-d)$. Assortative mating does not alter their values [3]. With panmixis within the sample, DD has the proportion d^2, DR the proportion $2dr$, and RR the proportion r^2 in all strata.

Intermediate quantities. Suppose a and b are composed of three parts each, so that

$$a = e+f+g, \text{ and } b = h+i+k \qquad (1), (1a)$$

Within the two generations, the proportions e and h represent the zygotrant individuals of the genotype DD, f and i the zygotrant DR-individuals, g and k the zygotrant RR-individuals.
We then have the (uncorrected) zygotrance values

$$\text{for DD: } \frac{e}{d^2} \text{ and } \frac{h}{d^2} \qquad (2), (2a)$$

$$\text{for DR: } \frac{f}{2dr} \text{ and } \frac{i}{2dr} \qquad (3), (3a)$$

$$\text{for RR: } \frac{g}{r^2} \text{ and } \frac{k}{r^2} \qquad (4), (4a)$$

We obtain the genetrance values in the following manner. The proportions e and h consist entirely of D-factors, that also fill up half of the proportions f and i (cf. diagram 2). Those genetrant D-factors may conveniently have their own proportion symbols m and s, so that

$$m = e+\tfrac{1}{2}f, \text{ and } s = h+\tfrac{1}{2}i \qquad (5), (5a)$$

The remaining part of genetrant factors are R-factors, forming

$$a-m = n = \tfrac{1}{2}f+g, \text{ and } b-s = t = \tfrac{1}{2}i+k \qquad (6), (6a)$$

Consequently we define the genetrance values

$$\text{for D: } M = \frac{m}{d} \text{ and } S = \frac{s}{d} \qquad (7), (7a)$$

$$\text{for R: } L = \frac{n}{r} \text{ and } T = \frac{t}{r} \qquad (8), (8a)$$

Since it seems practical to gather in one place most of the symbol apparatus some simplifications may be accounted for here:

$$(I) = a^2 \frac{A_{I2}}{N_{I2}} \qquad (9)$$

$$(II) = 2a(1-a) \frac{A_{II2}}{N_{II2}} \qquad (10)$$

$$(III) = (1-a)^2 \frac{A_{III2}}{N_{III2}} \qquad (11)$$

$$C = \frac{2(I)+(II)}{b} = 1 - \frac{(III)-(I)}{b} = 2 - \frac{2(III)+(II)}{b} \qquad (12)$$

5. The general formula of monohybridic diallelomorphic penetrance

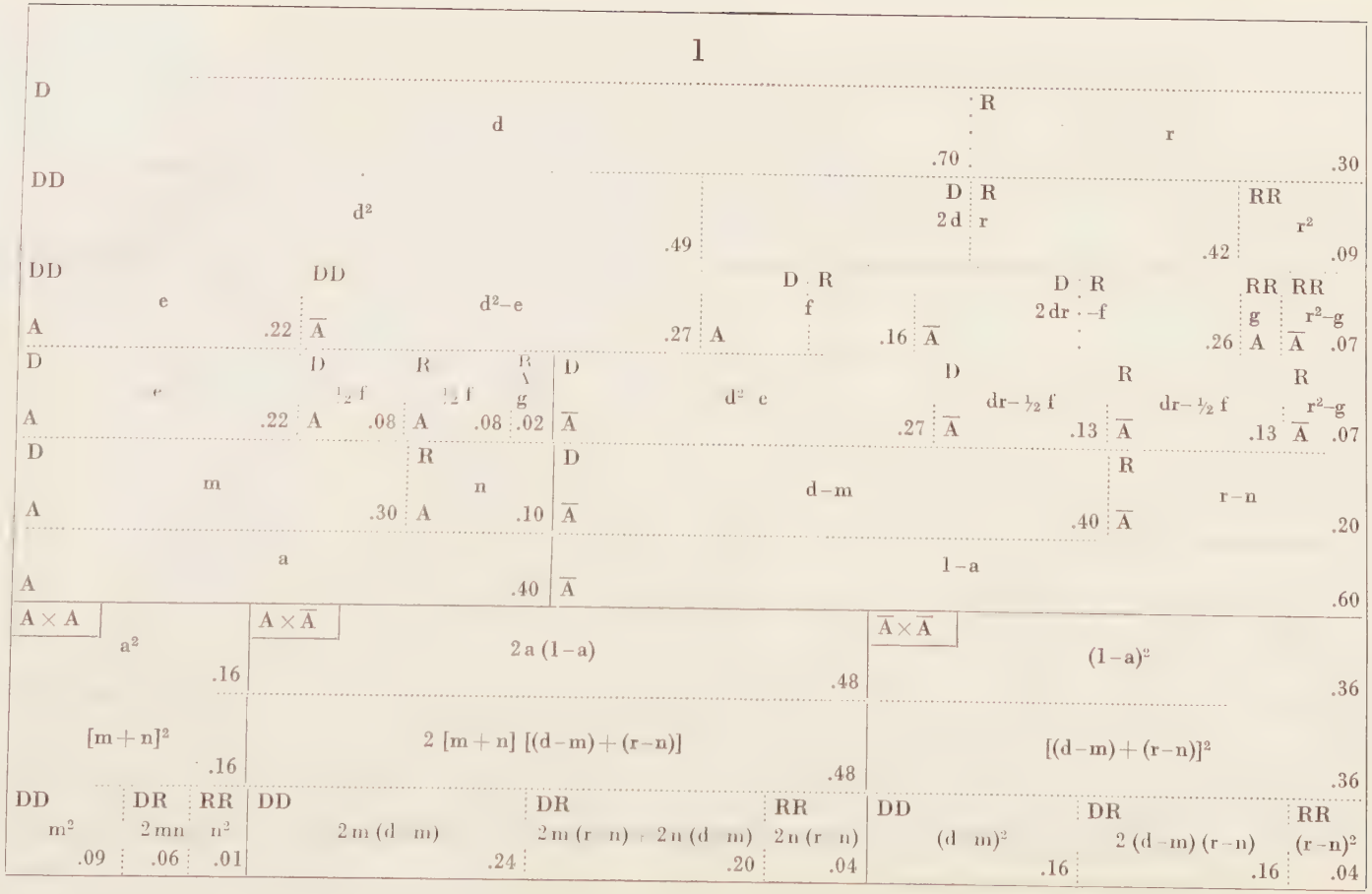
By means of the method devised by *Trankell* we are now able to construct the general formula for penetrance in monohybridic diallelia. This formula describes the passing of gene-factors from generation to generation, from phenotype to phenotype. Relative population diagrams similar to diagram 2 will facilitate considerably the understanding of the mechanism.

The upper part of diagram 2 describes a single generation (with the arbitrary values: $d = .70$; $e = .22$; $f = .16$; $a = .40$) from different points of view. The first row gives the relative size, the second row the gene-factor proportions, the third row the proportions of genotypes, the fourth row the proportions of A-zygotrants and $\bar{A}$-zygotrants. In the fifth row we arrange first proportions of A-genetrants, then proportions of $\bar{A}$-genetrants. The sixth row repeats the same proportions in simplified form. The seventh row gives the phenotypical aspect of the generation considered. Here is the starting point for the crossing pictured in diagram 1 and in the last three rows of diagram 2.

In A × A-matings, the gene-factors will combine according to $(m - n)^2$. Within the a^2-fraction of N_2, therefore, the genotypes DD, DR and RR appear with the following proportions: m^2; $2mn$; n^2. Within the fraction $2a(1-a)$ they have the proportions: $2m(d-m)$; $2m(r-n) - 2n(d-m)$; $2n(r-n)$. Within the last N_2-fraction, $(1-a)^2$, their proportions are: $(d-m)^2$; $2(d-m)(r-n)$; $(r-n)^2$.

Only some DD become trait-carriers, namely $\frac{h}{d^2}$ of that genotype in N_2 (cf. 2a). We may then expect $\frac{h}{d^2}\, m^2$ A-zygotrant DD: s; $\frac{i}{2dr}\, 2mn$ A-zygotrant DR: s; and $\frac{k}{r^2}\, n^2$ A-zygotrant RR: s in the a^2-fraction of N_2. The sum of those proportions has the same relation to a^2 as has A_{I2} to N_{I2}. In an analogous manner we find the ratio between A-zygotrant children and all children within the other two types of families, A × $\bar{A}$ and $\bar{A}$ × $\bar{A}$. We thus arrive at the following equation system.

$$\frac{A_{I2}}{N_{I2}} = \frac{1}{a^2}\left(\frac{h}{d^2}\, m^2 + \frac{i}{2dr}\, 2mn + \frac{k}{r^2}\, n^2\right) \qquad (13)$$


1
D
d
.70
R
r
.30
DD
d²
.49
D
2d
R
r
.42
RR
r²
.09
DD
e
A
.22
Ā
DD
d²–e
.27
D R
f
A
.16
Ā
D R
2dr –f
.26
RR RR
g r²–g
A Ā .07
D
e
A
.22
Ā
D R R
½f ½f g
A .08 A .08 A .02
Ā
D
d² e
.27
D R R
dr–½f dr–½f r²–g
Ā .13 Ā .13 Ā .07
D
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R
n
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.10
Ā
D
d–m
.40
R
r–n
Ā
.20
a
A
.40
Ā
1–a
.60
A×A
a²
.16
A×Ā
2a(1–a)
.48
Ā×Ā
(1–a)²
.36
[m+n]²
.16
2[m+n][(d–m)+(r–n)]
.48
[(d–m)+(r–n)]²
.36
DD DR RR
m² 2mn n²
.09 .06 .01
DD
2m(d–m)
.24
DR RR
2m(r–n) 2n(d–m) 2n(r–n)
.20 .04
DD DR RR
(d–m)² 2(d–m)(r–n) (r–n)²
.16 .16 .04

$$\frac{A_{II2}}{N_{II2}} = \frac{1}{2a(1-a)}\left[\frac{h}{d^2}2m(d-m) + \frac{i}{2dr}\Big(2m(r-n) + 2n(d-m)\Big) + \frac{k}{r^2}2n(r-n)\right] \quad (14)$$

$$\frac{A_{III2}}{N_{III2}} = \frac{1}{(1-a)^2}\left(\frac{h}{d^2}(d-m)^2 + \frac{i}{2dr}2(d-m)(r-n) + \frac{k}{r^2}(r-n)^2\right) \quad (15)$$

This is the general equation system for penetrance in monohybridic diallelia. To the left, we account for the found quotients, to the right, for the expected ones.

The system contains four unknowns: d, m, h, and i. All other values are observed or derived. Moreover, each equation is derived from the other two equations, so that they together form an identity. If we move the leading inverted coefficient from the right to the left, so that we get $\frac{A_{I2}}{N_{I2}}a^2 = \ldots$. etc., and then sum the right members the result will amount to b, and all the unknowns have disappeared. The right members really form a system of horizontal, vertical, and diagonal squares, easier to see from the following simplified transformation (especially if we write $\frac{i}{2}\cdot 2$):

$$(I) = hM^2 + iML + kL^2 \quad (16)$$

$$(II) = h2M(1-M) + i[M(1-L) + L(1-M)] + k2L(1-L) \quad (17)$$

$$(III) = h(1-M)^2 + i(1-M)(1-L) + k(1-L)^2 \quad (18)$$

Attempts to solve the equations in their general form are hopeless, as long as we have only two equations to work with and have found no way to reduce the number of unknowns. Such a reduction, on the other hand, is possible as soon as we adapt the formula to any of the remaining nine cases of table 1. Cases with two plus-signs in that table have three unknowns, cases with one plus-sign only one unknown. It was a case of the last-mentioned type that originally inspired *Trankell* to construct, after several fruitless trials, the first simple model of the calculus.

In complete zygotrance we find $e = d^2$ (2), $f = 2dr$ (3), or $g = r^2$ (4). For $e = d^2$, for instance, $g = a-f-d^2$ (1). Under the hypothesis of missing zygotrance in DD, we have $e = 0$ and $g = a-f$. For the case (1 + 0) we have $h = d^2$, $i = b - d^2$, and $s = \frac{1}{2}(b+d^2)$ according to (5a), so that only one unknown, d, remains if we construct m analogously to s.

In passing, we may note that the empirical C-values of (12) may be described theoretically, by subtraction of (16) from (18), as

$$C = 2L + \frac{2s(M-L)}{b} \quad (19)$$

The empirical C-value finds an application in the case (+ + 0), that is perfectly solvable. Before we proceed with the analysis of the general case and its limitations, it may be illuminating to consider the solution of (+ + 0).

6. The solution of the case of penetrance in DD and DR

The equation system for (+ + 0) is obviously the following one.

$$(I) = hM^2 + (b-h)\,ML \tag{20}$$

$$(III) = h\,(1-M)^2 + (b-h)\,(1-M)\,(1-L) \tag{21}$$

By solving h in (20) and inserting it into (21) we get an equation where C appears as a coefficient. We find the genetrance

$$M = \tfrac{1}{2}\left(C + \sqrt{C^2 - \frac{4(I)}{b}}\right) = \tfrac{1}{2}\left(C + \sqrt{(2-C)^2 - \frac{4(III)}{b}}\right) \tag{22), (23}$$

This empirical genetrance value presupposes panmixis in the sample: for correction, if necessary, see later. The real drawback is, however, that the three unknowns remain unsolved. We must add a third equation of adequate origin. It may be derived from the equations of the subsequent mating of N_2, where we determine S directly by means of (22) or (23) from the C-value of N_3. Since $s = \frac{1}{2}(b+h)$, we have $h = 2dS - b$ (7 a). Subtracting (20) from (21), we get:

$$h = b\,\frac{C-M-L}{M-L} = 2dS - b \tag{24), (25}$$

After substitution of L by $\frac{a-dM}{r}$, we finally arrive at:

$$d = \frac{\frac{1}{2}\,C\,a}{\frac{1}{2}\,C - M + \frac{S}{b}\,(M-a)} \tag{26}$$

Now, the knot of (+ + 0) is untied, and it is easy to wind up the thread. We may determine m and s (7, 7 a), e and h (25), L and T (6, 8, 6 a, 8 a), e_3 and M_3 of the third generation (24, 25), the two zygotrances in each generation (2, 3), and so on.

It seems useless to try to construct the two equation systems by means of only one mating. If we change the criteria in N_1 or N_2 we certainly get a new pair of equations with a new m- or h-value, but identities prevent the solution. In this connection, one should perhaps emphasize that the criteria of N_2 in the three-generation solution must not change: the trait A must be attributed to exactly the same individuals in their rôle of children in the first and of parents in the second mating.

Example. Since the author does not know of any material in population genetics that fills the requirements, the following example is purely fictitious and given only as a demonstration of the method. Suppose we find the trait A in 10 per cent of the grandparents, in 20 per cent of the parents, and in 30 per cent of the children. That is, $a = .10$; $b = .20$; $a_3 = .30$. We also know the quotient of trait-carriers among the children in each family group $A \times A$, $A \times \bar{A}$, $\bar{A} \times \bar{A}$. These nine values are known. Unknown are: $d = .40$; $e = .08$; $h = .12$; $e_3 = .15$, as well as the values derived from them: $m = .09$; $s = .16$; $M = \frac{9}{40}$; $L = \frac{1}{60}$; $S = \frac{16}{40}$; $T = \frac{4}{60}$.

The first equation has the (unknown) construction:

$$(I) = .12\,(\tfrac{9}{40})^2 + (.20 - .12) \cdot \frac{9}{40} \cdot \frac{1}{60} = \frac{.0765}{12}$$

The quotients we could expect in the material would be:

$$(I) = \frac{.0765}{12};\ (III) = \frac{1.5965}{12};\ (I)_3 = .028;\ (III)_3 = .138.$$

We now find:

$$C = 1 - \frac{1.5965 - .0765}{12 \cdot .20} = \frac{11}{30}, \text{ and } C_3 = 1 - \frac{.138 - .028}{.30} = \frac{19}{30}.$$

By means of (22) we get $M = \frac{9}{40}$ and $S = \frac{4}{10}$.

The gene-factor proportion (26) is:

$$d = \frac{\frac{11}{60} - .10}{\frac{11}{60} - \frac{9}{40} + \frac{.40}{.20}\left(\frac{9}{40} - .10\right)} = .40.$$

Successively, we get:

$$m = .40\ \frac{9}{40} = .09;\ s = .40\ \frac{4}{40} = .16;\ e = 2\,(.09) - .10 = .08;\ f = .10 - .08$$

$$= .02;\ h = 2\,(.16) - .20 = .12;\ i = .20 - .12 = .08;\ T = \frac{.20 - .16}{1 - .40} = \frac{4}{60};$$

$$e_3 = .30\ \frac{\frac{19}{30} - \frac{4}{10} - \frac{4}{60}}{\frac{4}{10} - \frac{4}{60}} = .15.$$

7. *Some functions in the case* $(+\ +\ +)$.

The solution of the general case of penetrance in monohybridic diallelia has not succeeded, since we start with four unknowns and two more are added with every mating. Even the genetrance values

escape calculation. The reason is obvious, if we construct the general formula for the root-expression in (22) by inserting the general C-value of (19) and the general (I)-value of (16):

$$\tfrac{1}{2}\left(C \pm \sqrt{C^2 - \frac{4\,(I)}{b}}\right) = L + \frac{M-L}{b}\left(s \pm \sqrt{s^2 - bh}\right) \qquad (27)$$

Under the hypothesis of $(+\ +\ 0)$, where $s = \tfrac{1}{2}\,(b+h)$, it resolves very smoothly into the plus-form M, whereas the minus-form takes the shape of $\frac{(I)}{bM}$. In the case of $(+\ +\ +)$, on the other hand, the expression runs into varying kinds of values, inter alia complex values as soon as $hk > (\tfrac{1}{2}\,i)^2$.

As a curiosity, at least for the time being, one might regard the following general equation for d:

$$d^3 - 2d^2 + (1+u)\,d - u = 0 \qquad (28)$$

It was found in the course of rather extensive calculations concerning the otherwise uninteresting case of $i = \tfrac{1}{2}\,b$. Because of that restriction, it was possible to derive a formula for u that closely resembles (26). In the general case, this is impossible, but (28) nevertheless holds. Its roots are: d; r; 1; while u has the value dr.

8. Penetrance formulae solvable in two generations

The cases $(1\ +\ 0)$, $(+\ 0\ 0)$, $(0\ +\ 0)$, and $(0\ 1\ +)$ of table 1, as well as their inversions, require only two generations as a basis of calculation. In his first paper on the topic of penetrance calculus, *Trankell* [7] derived the formulae for $(1\ +\ 0)$ and $(+\ 0\ 0)$. Both cases give a system of three separate equations with one unknown, the systems being of the fifth degree in the former case, of the second degree in the latter case. Under the hypotheses $(1\ 0\ 0)$ and $(1\ 0\ 1)$, population genetics is not needed at all, which is probably the reason why dominants and hybrids have attracted relatively much attention in genetics.

9. Correction for sample deviation from isofertility and panmixis

If deviation from isofertility occurs within the sample, all proportions have to be corrected. Deviations from panmixis require correction of the proportions of zygotes: d^2, $2\,dr$, and r^2 in the zygotrance quotients of (13), (14), (15).

When the average number of children happens to vary from family group to family group we will find different d-proportions

in the generations. Since the situation arises when brothers and sisters are added to a representative children sample, it is reasonable to regard the d-value of the children, their parents and grandparents as the closest approximation to the population value. We may use the distorted d′ of N_3 in all generations, if we distort them accordingly by assuming that each N_3-child has its own couple of parents, so that the parents number $2N_3$ instead of N_2. (Distorted values carry the sign: ′.) Since each N_{I3}-child has two A-parents and each N_{II3}-child one A-parent, we have

$$b' = \frac{2N_{I3} + N_{II3}}{2N_3} \tag{29}$$

Although the chances to find D-genes have altered within the distorted population they remain unchanged within the phenotypical groups A and $\bar{A}$. Looking at diagram 2 we find that

$$\frac{m}{a} = \frac{m'}{a'} \text{ and } \frac{d-m}{1-a} = \frac{d'-m'}{1-a'} \tag{30), (31}$$

Therefore,

$$d = \frac{a}{a'}\,m' + \frac{1-a}{1-a'}\,(d'-m') \text{ and } r = \frac{a}{a'}\,n' + \frac{1-a}{1-a'}\,(r'-n') \tag{32), (33}$$

For $(+\,+\,0)$, we may determine h in the regular way (24) for the first mating and h′ (25) for the distorted proportions of the second mating. We then transform one of them into the terms of the other one, for instance (cf. diagram 2) in the following way:

$$h = \frac{b}{b'}\,h' = \frac{b}{b'}\left[2S'\left(\frac{b'}{b}\,dM + \frac{1-b'}{1-b}\,(d-dM)\right) - b'\right].$$

Equalling this h to that of (24), we arrive directly at the correct d-value.

Usually we do not find strict panmixis in the sample. Suppose the proportion va^2 of the parents forms concordant matings (cf. diagram 1), the rest: $(a-va^2)$ goes to discordant matings. A second proportion $(a\ va^2)$ is needed for the same reason from the $\bar{A}$-parents, so that $(1-2a+va^2)$ remains for the $\bar{A}\times\bar{A}$-mating. The chances to find D- or R-genes in A-parents do not change, neither do the proportions *within* the family group, although they have changed within the total population. The proportions of DD, DR and RR within va^2 are therefore: vm^2; $v2mn$; vn^2. In the discordant group $2a(1-va)$, that also may be written $\frac{1-va}{1-a}\cdot 2a(1-a)$, we find DD: $\frac{1-va}{1-a}\,2m\,(d-m)$; DR: $\frac{1-va}{1-a}\,2\left(m\,(r-n)+n\,(d-m)\right)$; RR: $\frac{1-va}{1-a}\,2n$

$(r-n)$. In the $\bar{A} \times \bar{A}$-group we find DD: $\frac{1-2a+va^2}{(1-a)^2}(d-m)^2$; DR: $\frac{1-2a+va^2}{(1-a)^2} 2(d-m)(r-n)$; RR: $\frac{1-2a+va^2}{(1-a)^2}(r-n)^2$. Summing all DD-proportions across the family groups and doing the same for the DR- and RR-proportions we find the population proportions to be:

$$\text{DD: } d^2 + \frac{(m-ad)^2(v-1)}{(1-a)^2} \tag{34}$$

$$\text{DR: } 2dr - 2\frac{(m-ad)^2(v-1)}{(1-a)^2} \tag{35}$$

$$\text{RR: } r^2 + \frac{(m-ad)^2(v-1)}{(1-a)^2} \tag{36}$$

We arrive at the v-value in the following manner, starting from any of the family groups, e.g. $va^2 = \frac{N_{I2}}{N_2}$. In isofertility, using (29), we have $v = \frac{N_{I2}N_2}{(N_{I2} + \frac{1}{2}N_{II2})^2}$ (37)

We can also, of course, calculate a^2 directly, if that appears more convenient. In passing, it may be mentioned that the expression $(m-ad)$ is a fraction of a genetrance difference: $dr(M-L)$.
If we write

$$V = \frac{(m-ad)^2(v-1)}{(1-a)^2} \tag{38}$$

the zygotrances of (2), (3), (4) take the following shape:

$$\frac{h}{d^2+V};\ \frac{i}{2dr-2V};\ \frac{k}{r^2+V} \tag{39), (40), (41}$$

These zygotrances may be used in the general equations (13), (14), (15), that in all other respects remain unchanged in the correction for assortative mating.

The equations for special hypotheses are easy to derive from the general formulae by modifying the h-, i- and k-values. In the case (1 + 0), for instance, $h = d^2 + V$ and $i = b - (d^2+V)$.

It is worth noticing that the correction for deviation from panmixis certainly changes h, i, k, and the total proportions of the genotypes, but it does not change the value of the zygotrance quotients nor the proportions of the genotypes within each family group (equation). Thus, the proportion of DD in the first group really is vm^2 within va^2, but by division we return to the original m-, n- and a-values of the basic equations.

Trankell [7] tried his (· 0 0)-hypothesis on the material from three American investigations of left-handedness published in 1913, 1928, and 1939. He was able to show, not only that the hypothesis fitted the raw material remarkably well, but also that all the gene-factor estimations were fairly alike. The r-values were in *Rife:* .401, .414, .439; in *Chamberlain:* .412, .393, .401; in *Ramaley:* .427, .427, .425. The author has corrected the values according to the methods indicated above. The result is: .404, .421, .416; .412, .393, .397; .4270, .4273, .4270. The differences have shrunk, especially between the second and third group, which are much larger than the first and therefore less sensitive to random variations.

Example. The material of *Rife* may serve in a demonstration of the two correction methods in combination. Left-handedness was found in 72 out of 1374 parents (a = .0524) and in 191 out of 2178 children (b = .0877). $A_{I2} = 6$. $N_{I2} = 11$. $A_{II2} = 34$. $N_{II2} = 174$. $A_{III\,2} = 151$. $N_{III\,2} = 1993$ [12].

The sample deviation from panmixis is obvious. N_1 should have been only 6, N_{II}: 216, N_{III}: 1956. The families further number 5, 62, and 620 couples, so that the fertility rates happen to be 2.2; 2.8; and 3.2 per couple in the different groups. We can now compute $a' = \frac{22 + 174}{2\,(2178)} = .0450$ from (29); $a'^2 = .0020$; $v' = \frac{11 \cdot 2178}{(11 + \frac{174}{2})^2} =$ 2.4946 from (37); since $m' = a'$ under the hypothesis (+ 0 0), we find $V' = \frac{(.045 - .045\,d')^2 \cdot (2.4946 - 1)}{(1 - .045)^2} = .0033\,(1 - d')^2$. Considering that in this case $h' = b$, we find that equation (14), for instance, takes the following corrected form: $\frac{A_{II2}}{N_{II2}} = \frac{b\,(d' - a')}{(1 - a')\,(d'^2 + V')}$, that is, $\frac{34}{174} = \frac{.0877\,(d' - .045)}{.955\,(d'^2 + .0033 r'^2)}$. This gives $d' = .417$. Ultimately, we see from (32) that $d = .0524 + \frac{.9476\,(d' - .045)}{.955} = .9923\,d' + .0077 = .421$.

10. The restriction of constant environmental factor pattern

At this stage of the analysis, it is possible to state the problem of environmental factors in more unambiguous terms than before. We may conveniently call the quotients of trait-carriers within the

family groups: P_I, P_{II}, P_{III} (in the notation of *Trankell* [13]: P_1, P_2, P_3). They correspond to the left members of the equations (13), (14) and (15).

Consider the case (0 0 +). Its zygotrance quotient is $\frac{b}{r^2}$ in all family groups, as long as we accept the restriction of constant environmental factor pattern. If we reject the restriction, we may add positive or negative values x, y, z (less than 1), so that the zygotrances read $\frac{b+x}{r^2}$, $\frac{b+y}{r^2}$ and $\frac{b-z}{r^2}$. The equations take the form:

$$P_I = \frac{b+x}{r^2};\ P_{II} = \frac{b+y}{r^2}\cdot\frac{r-a}{1-a};\ P_{III} = \frac{b+z}{r^2}\cdot\frac{(r-a)^2}{(1-a)^2} \qquad (42), (43), (44)$$

They obviously fulfil the condition:

$$\frac{P_I P_{III}}{(P_{II})^2} = \frac{(b+x)(b+z)}{(b+y)^2} \qquad (45)$$

Having thus changed the model, we may insert any r-values we like, and the zygotrances will vary accordingly. If we do not accept any specific gene-factors at all, we put $r = 1$, and the equations (42), (43), (44) take the form: $P_I = b + x$; $P_{II} = b + y$; $P_{III} = b + z$. This is the hypothesis of "pure" environmental effects, still subject to the condition (45).

If (45) is larger or smaller than unity, the hypothesis (0 0 +) is falsified. If (45) is equal to 1, three possibilities arise. 1. We are dealing with randomness, that is, $P_I = P_{II} = P_{III}$. 2. We are dealing with constant zygotrances, that is, $x = y = z = 0$. 3. We are dealing with environmental factors ($r \neq 1$), varying from group to group but forming a highly distinct pattern of the type $B_X : B_X B_Z : B_Z$, for instance 9:3:1. As long as no such factors have been shown to exist, the most likely theory is that of constant zygotrances.

Example. The three American investigations of left-handedness mentioned in section 9 gave values fairly close to 1, namely,

$$\textit{Ramaley:}\ \frac{6}{7}\cdot\frac{116}{953}\cdot\frac{170^2}{55^2} = .997;$$

$$\textit{Chamberlain:}\ \frac{7}{25}\cdot\frac{307}{7225}\cdot\frac{464^2}{53^2} = 1.082$$

$$\textit{Rife:}\ \frac{6}{11}\cdot\frac{151}{1993}\cdot\frac{174^2}{34^2} = .912.$$

The P-values are remarkably consistent, even if they are numerically smallest in *Chamberlain*, about twice as large in *Rife* and thrice as large in *Ramaley*, probably because of more or less generous

criteria. The deviation from 1 is small, which undeniably is a bit lucky if we consider how random variations of the small numbers in the A × A-groups might affect the value. The P_I-, P_{II}- and P_{III}-values form a pattern closely resembling $7:\sqrt{7}:1$, with a χ^2 of 48.8 in *Ramaley*, 75.1 in *Chamberlain* and 52.5 in *Rife*, all significant on the .001-level for df 2.

11. Possibilities and limitations of the penetrance calculus

The calculus founded by *Trankell* is still incomplete. It remains to investigate its possibilities regarding other genetic hypotheses, e.g. polyhybridic connections. Formulae of significance have to be worked out in order to make the conclusions statistically impeccable [14, 15].

An advantage of the calculus is the perspicacity of its concepts, laid down in quantitative mathematical terms. No wonder then that it reveals the rather narrow limits of our biological thinking. In return for the loss of some far—reaching vistas, however, we may hope to grasp a solid fact or two from time to time.

Among the limitations we find the basic hypotheses of section 2. A corollary of the theory may be mentioned here. Our concepts of penetrance presuppose some restrictions upon the concept of "gene". The word means at least two things. One is observable in the microscope: the chromomere. It is only one of the phenotypical manifestations of the "gene" in another and far wider sense: the gene-factor. This is a non-observable, multipotential factor belonging to the same "domain" [9] as genotype and environmental factors, as opposed to phenotype and to environment. (An extensive discussion of the concept of environmental factors or "mesotype" is excluded from this paper, like many other parts of the preliminary work, in order to avoid too long excursions within the complicated topic of penetrance.) We must not consider the gene-factors as simply factors "for" some trait. More often, they seem to modify the effects of the total genotype. This model of thought lies behind $(- - - -)$, where both A and $\bar{A}$ are supposed to penetrate whether D or R are present or not. In the $(+ + 0)$-hypothesis, on the other hand, D is supposed to be an obligatory condition for A, whereas it is not even necessary to call R a modificator here. The effect $\bar{A}$ penetrates partially in DD but completely in RR, as if R were an "empty" factor, allowing the total genotypical effect to pass without resistance. If we accept the hypothesis of $(+ 0 0)$ in the case of

left-handedness, we postulate that left-handedness is connected with a diallelomorphic gene-factor, right-handedness with the total genotype.

One important function of the penetrance calculus has not been mentioned as yet: the falsification of hypotheses. When a certain gene-factor is an obligatory condition for genetrance, viz. in the cases (+ + 0), (1 + 0), (+ 1 0) (+ 0 0), and (1 0 0), we may use M to falsify hypotheses—an operation which is often rather neglected but nevertheless necessary in the construction of proofs.

Example. The values of *Ramaley* lead to an M-value of about .2, so that m is about .2 d, while a = .08. In the case (1 + 0) we have $m = \frac{a + d^2}{2} = dM$, leading to a grossly imaginary d-value. In (+ 1 0) we arrive at a 2 dr-value of about .13, which would require an a-value of that size of more. The material immediately falsifies (1 0 0), and of course (1 1 1), since the zygotrance is incomplete in the homozygotes. For (+ 0 0) we arrive at an uncorrected d-value of about .4, in fair accordance with the more exactly computed .427.

In order to falsify (0 + 0) and (0 1 0), we may start from (+ + 0), where $m = \frac{1}{2}(e + a)$, according to (5). Obviously, $m_{max} = a$, that is, when only DD zygotrates, and $m_{min} = \frac{1}{2}a$, that is, when only DR zygotrates and e = 0. Via m = dM we arrive at $d_{max} = .40$ and $d_{min} = .20$. The latter applies to (0 + 0) and to its subhypothesis (0 1 0). Their first equation, $(I) = \frac{b}{2\,dr} \cdot 2mn$, where 2 dr = .32 and m = n = .04, would require b = .55, which falsifies both hypotheses (as well as the fact that b = .1566, really).

There remains (+ + 0). In principle, it is valid until we have determined the two zygotrances by means of two consecutive matings, as shown in section 6. Even here, though, M may yield some guidance. By inserting (8) and (6) into (24) we get the transformation $h = \frac{C - M - a}{M - a} b + \frac{2M - C}{M - a} bd$. If 2 M − C ≥ 0, we obtain the maximum value h = b. This occurs when the radical quantities of (22) and (23) have the sum of zero. With the numbers of *Ramaley* we get for the first and the third group .142958 — .141422 = .001536, for the first and the second group .141292 — .141422 = — .000130, for the second and the third group .655850 — .657257 = — .001407. The sum of sums is zero, which is a strong indication that we deal with random variations around the zero value in each case. If 2 M had been larger than C, namely, we should have found

positive sums everywhere, and, consequently, a sum of sums larger than zero. We find ourselves, therefore, in the favorable position of being able to show that h > b in *Ramaley*'s case. We have reason to think that the hypothesis (- - 0) is probable only on the condition that the heterozygotrance is zero, that is, under the special hypothesis (+ 0 0).

It does not seem feasible to treat the two remaining hypotheses (+ 0 +) and (+ + +) in a similar manner. Their C-expressions in accordance to (19) and (27) are complicated, partly complex. We should then accept them as possible alternatives to their subhypothesis (- 0 0), all within the frame of their common hypothesis: monohybridic diallelia. Nevertheless, *Trankell* seems justified in stating that his findings confirm the hypothesis that left-handedness is determined by a recessive gene-factor, penetrant in connection with co-determining environmental factors. The confirmation lies in the following facts: 1. a highly specialized hypothesis explains the findings with remarkable accuracy, 2. any environmental-factor-hypothesis (in connection with an equivocal genotype) should have to cover also the (- 0 0)-mechanism, which seems unlikely, 3. out of nine genetic side-hypotheses seven have been falsified, while the eighth is curious and far-fetched, and the ninth is possible but so general, that it would in itself be a curious thing if the general hypothesis should happen to duplicate its own subhypothesis along another path. (It is, on the other hand, obvious that the hypothesis does not cover the case of left-handedness in monozygotic twins [14], where it is likely that genotypical asymmetries play an important rôle, as *Dahlberg* [4] suggests.)

The penetrance calculus will probably be useful also in the study of environmental factors. In genetics, they have mostly been investigated in completely penetrant homozygotes (in different environments) and in their experimentally produced heterozygotes, the latter often being especially sensitive to environmental variations. Since human genetics has no access to experiments, we do not always even know whether a certain phenotype is a homozygote or a heterozygote. In cases where we have reason to suspect that one of two alternative phenotypes is tied to one of two gene-factors: (+ - 0), we now have the chance to determine the proportions of 1. gene-factors, 2. genotypes, and 3. zygotrances. Most important of those are the zygotrances, since we may let them vary by means of extrinsic stimuli. Until now, such zygotrances have been studied only in the form of mixed homo- and heterozygotrances, whereas

we now have the opportunity to study the more sensitive part separately, in their f-values.

The penetrance calculus may also prove helpful in making the nature-nurture-problem more generally understood, since its mathematical terms define some functions of the problem in an exact manner. Confusion is apt to arise out of such statements as: "this disease (phenotype) is caused by heredity (gene-factors) to 65 per cent, and by environment (environmental factors) to 35 per cent." We might express the problem more appropriately thus: "within a certain pattern of environmental factors, past and present, how large is the homo- and how large the heterozygotrance?"

Another field of genetics, hitherto almost inaccessible, will perhaps open up to the calculus. The multiple effects of a gene-factor may zygotrate, some in a high, some in only a slight degree. If the gene-factor is one out of a monohybridic pair, each effect will lead to the same gene-factor proportion. Even in the $(+ + 0)$-case, two generations will provide us with sufficient data to allow a good guess. Starting from A_1 we may proceed to A_2 in one phase of the investigation, to another trait B_2 in another phase. Two parallel equation systems will arise, each leading to the same M if the gene-factor is common to A and B, although the apparent correlation between A and B may be very slight, even negative, in the raw material.

Also in the fields of experimental genetics, medicine, abnormal and normal psychology, ecology, and other biological sciences we may hope to widen our spheres of knowledge by means of the penetrance calculus, since it allows us to evaluate simultaneously the influences of gene-factors, total genotype, and environmental factors, all of which are of a non-phenomenological nature.

Summary

The penetrance calculus of *Trankell* is presented in general formulae, applicable to monohybridic diallelia. The author gives the solution of the case when one of the gene-factors is obligatory in the trait-carriers. This solution is impossible in principle without investigation of three subsequent generations. Correction methods are given for deviation from panmixis in the population and from isofertility within the sample. A discussion of the concept of penetrance leads to a partition into two distinct sets, called genetrance and zygotrance. Genetrance refers to the ratio of the manifested to the total quantity of a certain gene-factor in the population.

Zygotrance refers to the ratio of the manifested to the total quantity of a certain genotype in the population. Mathematical definitions of the two kinds of concept are presented. Both kinds vary with environment factors and total genotype, the genetrance moreover with the mutual proportions of diallelomorphic genotypes. The author discusses, in a concluding section, possible fields of application of the calculus and exemplifies by testing a hierarchy of hypotheses concerning a material of concrete genetic findings.

Résumé

Les calculs de pénétrance de *Trankell* sont exposés en formules générales, applicables à la diallélie monohybride. L'auteur présente la solution du cas où l'un des facteurs géniques se trouve obligatoirement chez les porteurs d'un certain trait. Cette solution est en principe impossible sans l'investigation des trois générations suivantes. Il indique des méthodes de correction pour les cas où il existe une déviation soit de la panmixie dans la population, soit de l'isofertilité dans le même groupe. Une discussion sur la notion de la pénétrance aboutit à une séparation en deux catégories distinctes, l'une appelée «génétrance», l'autre, «zygotrance». La «génétrance» se rapporte à la proportion de la quantité manifestée par rapport à la quantité totale d'un certain facteur génique dans la population. La «zygotrance» se réfère au rapport entre la quantité manifestée et la quantité totale d'un certain génotype dans la population. L'auteur donne des définitions mathématiques des deux notions. L'une et l'autre varient selon les facteurs du milieu et le génotype total, la «génétrance» en outre avec les proportions mutuelles des génotypes diallélomorphes. L'auteur discute, dans ses conclusions, les champs d'application possibles des calculs en question et les illustre d'un exemple en soumettant à un test une hiérarchie d'hypothèses concernant un matériel de données génétiques concrètes.

Zusammenfassung

Trankells Penetranzkalkül wird in allgemeinen Formeln, die sich auf monohybride Diallelie beziehen, dargelegt. Verfasser gibt die Lösung jenes Falles an, wo der eine Genfaktor bei den penetranten Merkmalsträgern obligat ist. Diese Lösung ist prinzipiell unmöglich, bis man drei aufeinanderfolgende Generationen einer Population untersucht hat. Verfasser gibt ferner Methoden zur Korrektion der eventuellen Abweichung von Panmixie in der

Population und von Isofertilität innerhalb des Materials. Erörterungen über den Penetranzbegriff führen zu einer Zerlegung in zwei scharf geschiedene Begriffe: Genetranz und Zygotranz. Genetranz bezieht sich auf den Quotienten zwischen dem manifestierten und dem totalen Anteil eines bestimmten Genfaktors in der Population. Zygotranz bezieht sich auf den Quotienten zwischen dem manifestierten und dem totalen Anteil eines bestimmten Genotypus in der Population. Beide Begriffe werden mathematisch definiert. Sie wechseln quantitativ mit Milieufaktoren und totalem Genotypus, die Genetranz zudem mit den Proportionen der verschiedenen diallelomorphen Genotypen. Verfasser verweist zum Schluß auf geeignete Verwendungsgebiete des Penetranzkalküls und liefert ein Beispiel von planmäßiger Auswahl innerhalb eines Systems von Hypothesen über bekannte Erblichkeitsbefunde.

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Author's address: Dr. Carl-Gustaf Berglin
Dept. of Public Health,
Burggrevegatan 11, *Göteborg* (Sweden).

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From The University Institute for Human Genetics
(Chief: Professor Tage Kemp, M.D.)
and The Finsen Institute and Radium Center, Central Laboratory
(Chief: Mogens Faber, M.D.)

HEREDITARY TRANSIENT MUSCULAR PARALYSIS IN DENMARK. GENETIC ASPECTS OF FAMILY PERIODIC PARALYSIS AND FAMILY PERIODIC ADYNAMIA

By HANS FR. HELWEG-LARSEN,
M. HAUGE and UFFE SAGILD

Recent studies (*Sagild* and *Helweg-Larsen* [1955]) suggest that the hereditary forms of transient muscular paralysis may be separated into at least two groups: Family periodic paralysis and family periodic adynamia. The distinction is based on:

1. The clinical manifestation of the attacks: Family periodic paralysis is characterized by rather infrequent, but fairly severe attacks of muscular paralysis, which may last for 2–3 days. By contrast, family periodic adynamia shows frequent attacks of short duration (15–30 minutes).

2. Hypopotassemia is characteristic of the attack of periodic paralysis, whereas periodic adynamia may show hyperpotassemia during the attack.

3. Attacks of family periodic paralysis respond favourably to treatment with potassium salts, whereas administration of potassium in cases of family periodic adynamia will *provoke* an attack (*Gamstorp* [1954], *Sagild* [1955]).

4. *Genetically*, the two types of transient muscular paralysis seem to present different modes of inheritance:

Family periodic paralysis shows irregular dominant inheritance with almost complete sex-limitation to males. Periodic adynamia, on the other hand, is inherited as a regular dominant character. This statement will be further elucidated below. An analysis of the linkage relations and a review of the clinical and biochemical findings in the two disorders will be reported separately.

Methods

The material for the present study was obtained as follows:

1. The genealogical studies already published of Danish families with transient muscular paralysis were extended.

2. All Danish neurologists and the general practitioners in some parishes in the southern part of Jutland were asked to report cases of transient muscular paralysis.

3. A few cases of the disorder were obtained by reports from hospitals to the University Institute for Human Genetics.

The index cases thus obtained were questioned as to their relatives and possible cases in the family. All living siblings of affected individuals were interviewed personally by the authors for the purpose of disclosing secondary cases among the sibs and their offspring. The cooperation of the families was excellent.

The genealogical information received was checked by the aid of birth registers, census registers and census lists.

The ascendencies of the patients were traced to the greatest possible extent in an attempt to reveal a common ancestor of the affected families.

The descendencies of suspected gene carriers in early generations were traced as far as possible (the Danish archives do not permit the tracing so far back and into the sidelines as do the Swedish archives).

In spite of our efforts we may not have found all the cases of transient muscular paralysis existing in Denmark. Generally only the rather severe cases are known by the relatives. In some instances the affected members of the elder generation will teach those affected of the next generation how to control the rate of attacks and how to treat the developing attack physically, by dietary measures, and by drugs. Accordingly the family doctor is usually not consulted in such cases, and he will not know of their existence. Besides, the disorders, being generally little known in medical circles, are often mistaken for neuroses or malingering.

Thus, direct tracing of the cases by relatives or doctors, as well as indirect search through archive studies leading to distant branches of the families are both inadequate.

Family Periodic Paralysis

Diagnosis

As a rule the diagnosis of periodic paralysis is easily established on the basis of a detailed past history. As far as possible, one or more

Table 1. Personal and clinical data of patients suffering from family periodic paralysis, and of some of their relatives.

Family number	Generation number	Individual number	Sex	Initials (at birth)	Year of birth (or at registration of birth)	Year of death	Occurrence of periodic paralysis	Age of manifestation	Maximal duration of attacks	Shortest interval between attacks	Cause of death or diagnosis of chronic disorder
I	1	1	m	C.S.C.	1876	1947	—	—	—	—	Prostatic carcinoma
I	1	2	f	J.M.J.	1881	1947	—	—	—	—	—
I	2	1	f	A.C.C.	1900	—	—	—	—	—	Possibly mild myotonic attacks
I	2	5	m	C.K.	1907	—	+	32	24 hours	years	—
I	2	6	m	M.K.	1904	1954	+	17	hours	weeks	Kyphoscoliosis, suicide
I	2	7	m	A.K.	1909	1923	—	—	—	—	"Brain inflammation"
I	2	8	m	O.E.K.	1911	—	+	16	72 hours	twice a week	—
I	2	9	m	G.E.K.	1913	—	+	25	24 hours	years	Kyphoscoliosis
I	3	21	m	T.K.	1936	—	+	16	72 hours	once a week	—
II	1	1	m	M.P.C.	1842	1902	—	—	—	—	Dropsy
II	1	2	f	A.M.M.	1841	1909	—	—	—	—	...
II	2	1	m	C.C.	1873	1901	+	14	...	...	Death in attack
II	2	3	m	H.M.C.	1880	1898	+	18	...	...	Death in attack
II	3	1	m	M.P.C.	1897	—	+	7	72 hours	once a week	Glaucoma
II	3	2	m	A.R.C.	1899	—	+	25	24 hours	months	—
II	3	3	m	H.M.C.	1900	—	+	18	24 hours	months	—
II	4	1	m	V.C.	1922	—	+	14	hours	...	—
III	1	1	m	J.J.N.	1845	1903	—	—	—	—	Heart disease
III	1	2	f	T.M.H.T.	1846	1919	—	—	—	—	Degeneration of heart
III	2	3	m	J.H.T.J.N.	1879	—	+	18	72 hours	months	—
III	2	4	f	R.E.E.N.	1883	—	+	65	18 hours	months	—
III	3	8	m	W.A.K.S.	1909	—	+	15	48 hours	4 years	Deaf mutism
III	3	10	m	J.E.F.H.S.	1911	—	+	17	8 hours	weeks	Feeble minded
III	3	13	m	S.H.S.	1918	—	+	14	72 hours	weeks	—
IV	1	1	m	J.B.A.	1791	...	...	...	...	...	..
IV	1	2	f	K.M.J.	1792	...	...	...	...	...	...
IV	2	3	f	K.M.B.	1825	...	?	...	...	...	...

Table 1 (cont.)

Family number	Generation number	Individual number	Sex	Initials (at birth)	Year of birth (or at registration of birth)	Year of death	Occurrence of periodic paralysis	Age of manifestation	Maximal duration of attacks	Shortest interval between attacks	Cause of death or diagnosis of chronic disorder
IV	3	6	f	J.C.S.	1856	1912	—	—	—	—	...
IV	3	9	m	J.C.S.	1862	1943	+	14	72 hours	weeks	Heart disease
IV	3	10	m	C.J.S.	1864	1893	+	17	...	...	Death in attack
IV	3	12	f	K.S.	1868	—	+	...	hours	...	—
IV	3	13	m	P.H.S.	1872	1892	+	18	...	...	...
IV	4	8	m	P.H.S.	1884	1953	+	16	12 hours	1 week	Cerebral hemorrhage
IV	4	10	f	K.M.S.	1890	—	+	13	72 hours	twice weekly	Graves' disease
IV	4	11	m	P.H.S.	1891	—	+	14	24 hours	twice weekly	—
IV	4	14	m	S.J.S.	1897	—	+	8	24 hours	1 week	—
IV	4	19	m	P.F.	1895	1921	+	19	days	months	Death in attack
IV	5	23	m	T.T.	1922	—	+	19	72 hours	1 week	—
IV	5	35	m	J.C.S.	1926	—	+	14	72 hours	2 months	Mental debility
IV	5	36	m	H.J.S.	1927	—	—	—	—	—	Epilepsy, mental debility
V	1	1	m	H.J.F.K.	1826	...	...	...	...	..	...
V	1	2	f	A.C.S.L.	1837	ca. 1900	...	...	...	...	...
V	2	1	f	A.S.K.	1857	1914	...	...	...	...	...
V	2	5	f	M.P.K.	1870	1926	...	...	...	...	...
V	3	1	m	H.K.	1878	—	+	70	36 hours	...	...
V	3	10	f	A.C.K.	1888	1944	—	—	—	—	—
V	3	11	m	N.P.L.	1894	—	+	35	3 hours	months	—
V	3	13	m	P.J.L.	1897	1916	+	...	...	...	Death in attack
V	3	14	m	A.R.L.	1902	—	+	...	...	...	Chronic criminality
V	3	19	m	A.D.L.	1910	—	+	9	48 hours	months	—
V	4	2	m	J.E.G.K.	1905	—	+	14	72 hours	months	—
V	4	8	m	C.P.K.	1921	—	+	19	36 hours	months	—
V	4	20	m	A.L.C.	1921	—	+	17	48 hours	1 month	—
V	4	21	m	E.C.	1923	1937	+	14	48 hours	1 month	Death in attack

Table 1 (cont.)

Family number	Generation number	Individual number	Sex	Initials (at birth)	Year of birth (or at registration of birth)	Year of death	Occurrence of periodic paralysis	Age of manifestation	Maximal duration of attacks	Shortest interval between attacks	Cause of death or diagnosis of chronic disorder
V	4	23	m	H.C.	1929	—	+	18	24 hours	...	—
V	5	1	m	H.K.	1931	—	+	22	8 hours	months	—
V	5	2	m	A.K.	1936	—	+	...	...	...	—
VI	1	1	m	J.S.	1794	1848	...	...	...	...	...
VI	1	2	f	S.I.	1799	1860	...	...	...	...	...
VI	2	3	m	S.J.S.	1832	ca. 1877	...	...	...	...	...
VI	2	5	m	I.S.	1837	1921	+	...	...	...	"old age"
VI	3	2	m	P.C.S.	1871	1944	?	...	...	...	?
VI	3	8	f	M.C.S.	1871	1931	+	?	24 hours	months	?
VI	3	9	m	J.P.S.	1873	1948	+	20	72 hours	...	Rectal carcinoma
VI	3	11	m	J.S.	1882	1932	+	17	72 hours	weeks	Perforated duodenal ulcer
VI	4	3	m	C.H.S.	1901	—	—	—	—	—	—
VI	4	9	f	J.M.	1899	—	—	—	—	—	—
VI	4	10	f	A.C.M.	1901	—	—	—	—	—	—
VI	4	11	m	I.M.	1903	—	+	22	8 hours	only once	—
VI	4	15	f	A.C.S.	1902	—	—	—	—	—	—
VI	4	16	m	A.S.	1903	1939	+	20	24 hours	months	Traffic accident
VI	4	33	m	J.S.	1920	—	+	34	48 hours	weeks	—
VI	5	2	m	P.C.S.	1938	—	+	16	36 hours	...	—
VI	5	11	m	H.H.	1923	—	—	—	—	—	Feebleminded
VI	5	14	m	W.H.	1927	—	+	18	hours	weeks	Feebleminded
VI	5	15	m	O.P.R.J.	1923	—	—	—	—	—	Psychopathia
VI	5	16	m	E.T.J.	1928	—	+	14	48 hours	1 week	—
VI	5	18	m	A.M.	1928	1950	+	18	24 hours	months	Death in attack
VI	5	20	m	E.M.	1934	—	+	19	2 hours	months	—
VI	5	37	m	H.J.	1926	—	+	19	48 hours	months	—

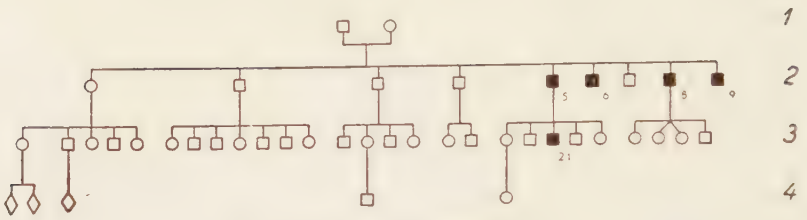

Fig. 1. Pedigree of Family No. 1.

Explanation to pedigrees.

- ● Affected female
- ∅ Female deceased in childhood
- □ Male gene carrier
- ◊ Unknown sex
- ② Two male siblings

members of each family were admitted to hospital (the Finsen Institute and the Radium Center) for extensive clinical and experimental investigation. No cases resembling periodic adynamia were found within the families with an obvious picture of family periodic paralysis, and difficulties of differentiation from other diseases (neurosis, *Graves*' disease) did not occur.

Material

Some of the most important clinical data of individuals suffering from the disorder are recorded in Table 1. In addition, the presence of chronic diseases and/or the cause of death are stated for some (apparently) non-affected members of the families. Each individual is characterized by the number of the family, the number of the generation as presented in the pedigrees (figs. 1–6), and the number within the generation.

The genealogical studies were more comprehensive than might appear from the pedigrees. A few genealogical remarks on each family may be appropriate:

Family I. Case I, 2, 8 has been described by *Kirk* and *Møller* [1933]. The ascendency of the first generation has been traced 3 or 4 generations further back. The grandparents of the first generation

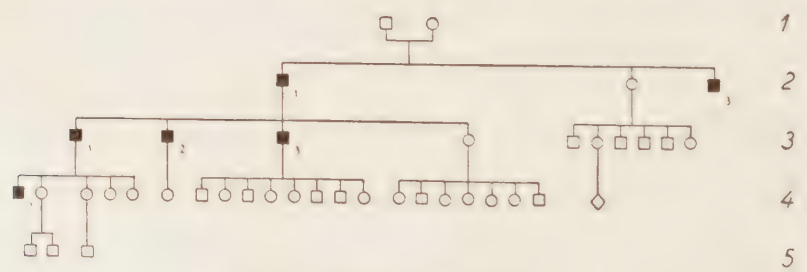

Fig. 2. Pedigree of Family No. 2.

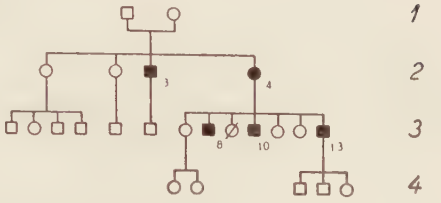

Fig. 3. Pedigree of Family No. 3.

all lived in northern Jutland, and connections to the southern part could not be demonstrated. A case of illegitimacy did, however, occur in the previous generation.

Family II. Case II, 3, 1 has been published by *Neel* [1929]. The ancestors of the first generation have been traced 2 or 3 generations further back. The grandparents of the first generation lived in the parish right in the center of the epidemic locality ("Gram") or in parishes just north of this place.

Family III. The ascendencies of the first generation have been traced 2 and 6 generations further back respectively. The grandparents of the male in the first generation came from the district between the towns of Silkeborg and Vejle in eastern Jutland. Of his wife's grandparents one had been born in Copenhagen, and one on the island of Bornholm.

Family IV. Case IV, 4, 8 has been described by *Vogt* [1918], and case IV, 4,14 is mentioned in the *Annual Reports of the Board of Forensic Medicine 1941*[1]. We have traced the ancestors 2 or 3 generations further back. The grandparents of the first generation all seem to have been born in South Jutland (*Gram* and *Gørding*).

Family V. The ancestors have been followed 2 generations further back. The grandparents of the first generation were farmers in the north-eastern part of Jutland, tradesmen on Greenland and in Holland, and possibly one couple lived as shopkeepers in southern Jutland.

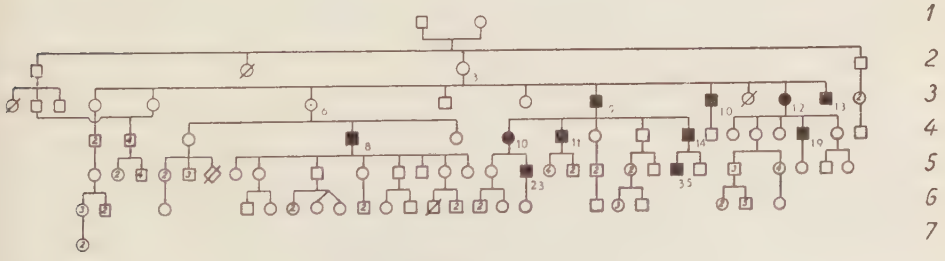

Fig. 4. Pedigree of Family No. 4.

[1] Retslægerådets årsberetning (1941).

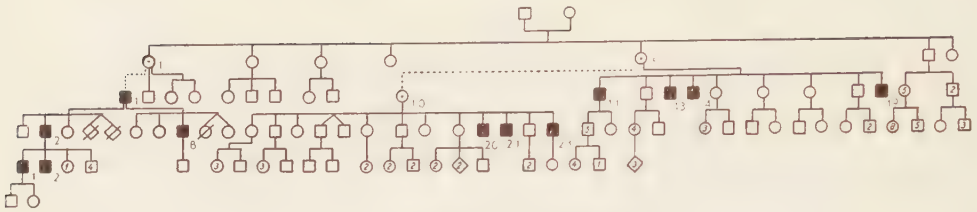

Fig. 5. Pedigree of Family No. 5.

Family VI. Case VI, 5, 37 was described by *Lundbaek* [1949] during the present investigation. Only the parents of the first generation have been found in the archives. They come from the parishes of Holsted and Føvling in the southern part of Jutland. Consanguinity within the direct ascendency of the propositi was demonstrated in none of the families reported.

Incidence in the population

Table 1 shows that in 1955 there lived 34 cases of family periodic paralysis in a population of 4,400,000, i.e. a prevalence rate of 0.8 per 100,000. Three more cases are recorded in Table 1 (II, 3, 3; II, 4, 1; and VI, 5, 14), but these patients have emigrated. As previously mentioned, we believe that some cases remain undiagnosed in spite of our efforts to reveal all cases in Denmark. The actual prevalence rate may, therefore, be higher.

Of the 34 patients living in this country at present 31 are males and 3 females. On the assumption of almost full manifestation of a dominant gene among males, the frequency of the gene is approximately 1.6 per 100,000.

Geographical distribution and problems of mutation

Fig. 9 shows the birth places of patients with periodic paralysis (and verified carriers of the gene) alive in 1950. The distribution of the cases gives a rather good impression of the present places of living. The majority of the cases are plainly seen to be localized in

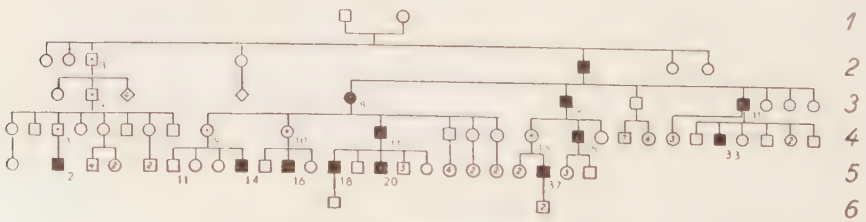

Fig. 6. Pedigree of Family No. 6.

Fig. 7.

Fig. 8.

Fig. 9.

Places of birth of Danish patients (and gene carriers) with family periodic paralysis being alive in 1850 (Fig. 7), in 1900 (Fig. 8), and in 1950 (Fig. 9).

the southern part of Jutland. In addition, two smaller colonies are seen: one in Copenhagen and another in northern Jutland.

The present geographical distribution may reflect migrations—particularly in the latter part of the 19th century. Figs. 8 and 7 analogously illustrate the geographical distribution of the gene in the years 1900 and 1850. In the last-mentioned year the three genes known to us (from families IV and VI) were localized approximately within the main district of the modern epidemic area. We are aware of the difficulties of mapping the location of the genes one hundred years back, the true gene carriers of the families I, II, III and V being unknown. However, the geographical distribution is probably

only slightly biased, because at least one member of the first generation of families II, III and V had been born in the center of the main epidemic district in southern Jutland (fig. 8). Family I is, perhaps, an exception, all known ancestors having been born in northern Jutland. The family may possibly be related to the remaining families either through the verified case of illegitimacy or through migration before year 1800.

Considering the spread of the gene in time and place as well as the irregular dominant inheritance of the disorder (vide infra), the Danish cases of family periodic paralysis seem more likely to originate from one or possibly two mutations than from at least five mutations (families II, III, IV, V, VI) having occurred almost simultaneously in the same part of the country, inhabited by only a small proportion of the total population. This conclusion implies that we consider the mutation rate for family periodic paralysis to be very low.

Severity and reproductive fitness

With a low mutation rate we should expect the fertility of affected individuals and healthy carriers to be nearly the same as in the general population. In fact, the affected individuals born within the interval between 1850 and 1899 had an average number of offspring of four—presumably the same as in the general population. Thus, despite occurrence of early death in paralytic attacks the general fertility of the affected remained uninfluenced in the present series.

Table 2 illustrates the severity of periodic paralysis. 7 cases of death in paralytic attack occurred among 14 affected persons dead from causes known to us.

Patients admitted to hospital for research purposes or for treatment of other diseases have been omitted from Table 2. The main

Table 2. Severity of family periodic paralysis expressed by number of fatal attacks or necessity of admission to hospital.

Age at investigation or death	No treatment or treatment by general practitioner	Hospital treatment	Death in attack	Total
15–34	13	3	7	23
35–54	9	4	–	13
≥ 55	14	2	–	16
Total	36	9	7	52

reason for hospitalization was severe attacks complicated by respiratory difficulties.

The table shows that the majority of cases are treated by the family doctor, if treated at all. This is also true for the fatal cases: of the 7 patients who died in an attack only one had been admitted to hospital before death. It appears from the table that fatal attacks occurred in the age group of 15–34 only. The mean age for death in attack in the present series was 22. Fatal attacks occurred in all families with a fairly large number of cases; and no appreciable differences were noticed between the individual families with regard to the severity of the disorder. The severity may vary considerably within the same family. Nothing can be predicted from the severity of the disease in a father regarding the severity of his sons.

Sex incidence and age of manifestation

The present study comprises a total of 52 patients with family periodic paralysis. Of these, 48 are males and 4 females. The sex ratio for *living* patients: 34 : 3 is, perhaps, a more reliable estimate of the true incidence of the disorder in the two sexes, because in our experience females become much less affected than males. Hence, the dramatic experiences of deceased male relatives may live on in the family traditions rather than the inconspicuous troubles of distant aunts. In our opinion, the low manifestation among the women living at present is real, being influenced but little by varying access to medical attention.

The low manifestation among women implies that the women must be in the majority among healthy carriers. Within our series we found 3 male and 7 female carriers, a ratio which does not quite correspond to the overwhelming number of female carriers expected. This may be due to insufficient tracing of all branches of the pedigrees under review.

The age at manifestation is given in Table 1. The age distribution is rather skew, ranging up to 70 years of age. The attacks rarely begin before the age of puberty. The median age of manifestation was 17 years in our series.

Inheritance

It is useless to compute a *Mendel*ian ratio within complete sibships owing to the very small number of female patients. By computing a *Mendel*ian ratio for males aged 20 years and over within sibships at risk, we get 50 affected or carriers among 105 males, i.e.

a *Mendel*ian ratio of 0.48. The ratio obtained is in full agreement with the hypothesis of dominant inheritance with a high rate of manifestation among males. In spite of the difficulty of demonstrating the presence of the gene among women we take it to be dominant with very low penetrance. The course of the genes in the pedigrees does not contradict this assumption. There is no evidence to suggest sex-linked inheritance.

Genetic hygiene

In the majority of our cases family periodic paralysis in its typical form causes only moderate disablement of the patients. Furthermore, the disorder can generally be treated with a good result as regards working capacity. We have observed only one case (VI, 5, 16) so severe that his working capacity could not be restored by ordinary treatment.

We have, therefore, followed a conservative line with regard to matrimonial advice and in questions of induced abortion or sterilization for eugenic reasons. In two cases we recommended sterilization: Case IV, 4, 14 because his sons were feeble-minded and one of them had periodic paralysis as well, and case VI, 5, 16 because of the severity of the case combined with an intelligence defect.

Family Periodic Adynamia

Diagnosis

The diagnosis of family periodic adynamia is easily made, even on the basis of a short interview. One symptom is almost pathognomonic: Practically all the patients have experienced difficulty in rising when having rested for a while after a period of hard muscular work. The patients have generally had the symptom since their school years, having been troubled by it during visits to church and movies, and when travelling by train.

Some patients with periodic adynamia have been admitted to hospital (The Finsen Institute and the Radium Center) for extensive clinical examination. Cases resembling family periodic paralysis have not been found within the family with periodic adynamia, and we have had no difficulties of differentiation from other diseases.

Material

To our knowledge, only one family (VII) with periodic adynamia exists in this country. Case VII, 6,11 has been described by *Neel* [1929]. The ascendency of the family has been traced to the

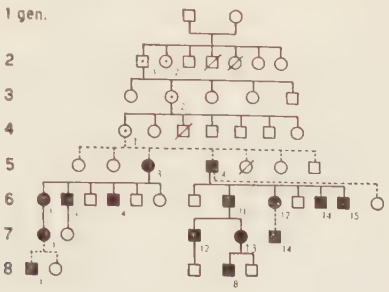

Fig. 10. Pedigree of Family No. 7.

same ancestors (VII, 1, 1 and VII, 1, 2) as a large Swedish family (the descendency of VII, 2, 2) with the same disorder, of which *Mjønes* [1954] and *Gamstorp* [1955] have given a preliminary description. The Danish branch of the family migrated to Copenhagen in the beginning of the 20th century. Another family with periodic adynamia, described by *Kulneff* [1902], lives in the southern part of Sweden. The question of a kinship between *Kulneff*'s family and the two branches of our family VII has not yet been clarified, according to *Gamstorp*.

Personal and clinical data on individuals exposed to periodic adynamia are recorded in Table 3, and the pedigree of the family is presented in fig. 10.

Frequency in the population

In 1955 the cases of periodic adynamia in Denmark numbered 5. Assuming that no other families exist with the disorder in this country, the prevalence rate and the gene frequency constitute 1 in 1,000,000.

Geographical distribution and problems of mutation

All the Danish patients live in Copenhagen. The family comes from the province of Blekinge (Sweden), close to or in the parish of Vånga. The family has spread over the neighbouring province of Skåne. The Copenhagen cases thus represent the western border of the present epidemic district.

The family of Kulneff lives only 25 miles from the birth place of cases VII, 5, 1–VII, 6, 12. No families with adynamia have been found elsewhere in Sweden. Several cases of illegitimacy occurred in the family in earlier days. Consequently we think it highly probable that the disorder in the family of Kulneff and in the branches of family VII is referable to a single mutation, which may have occurred before year 1740.

Table 3. Family periodic adynamia. Personal and clinical data on patients and some of their relatives.

Family number	Generation number	Individual number	Sex	Initials (at birth)	Date of birth (or at registration of birth)	Date of death	Occurrence of periodic adynamia	Age of manifestation	Maximal duration of attacks	Shortest interval between attacks	Cause of death or diagnosis of chronic disorder
VII	1	1	m	O.J.	1735	1808	...	...	...	...	...
VII	1	2	f	S.L.	1740	1810	...	...	...	...	...
VII	2	1	m	N.O.	1765	...	...	...	...	...	...
VII	2	2	f	T.O.	1767	...	...	...	...	...	...
VII	3	2	f	O.N.	1805	...	...	...	...	...	...
VII	4	1	f	A.T.	1829	...	...	...	...	...	...
VII	5	3	f	J.H.	1859	...	+	...	short	...	...
VII	5	4	m	O.L.H.	1863	1906	+	preschool	...	...	Gastric cancer
VII	6	1	f	F.S.	1893	—	+	preschool	30 min.	hours	—
VII	6	2	m	H.S.	1894	1929	+	preschool	30 min.	...	...
VII	6	4	m	S.S.	1896	1918	+	...	short	...	Influenza
VII	6	11	m	O.H.	1894	—	+	preschool	45 min.	...	...
VII	6	12	f	E.H.	1897	1925	+	preschool	short	...	Suicide
VII	6	14	m	B.F.H.	1902	—	+	7	hours	hours	—
VII	6	15	m	N.H.	1905	—	+	preschool	30 min.	hours	—
VII	7	1	f	F.M.	1918	—	+	preschool	1 hour	...	—
VII	7	12	m	J.E.H.	1924	—	+	preschool	30 min.	hours	—
VII	7	13	f	R.E.H.	1925	—	+	preschool	20 min.	hours	—
VII	7	14	m	E.A.H.	1922	—	+	preschool	hours	hours	—
VII	8	1	m	N.L.	1936	—	+	...	...	...	...
VII	8	8	m	D.S.	1949	—	+	18 months	15 min.	hours	—

Severity and reproductive fitness

Unlike in family periodic paralysis, death never occurs during a spontaneous attack of periodic adynamia. The disorder disables the patients when the attacks recur at intervals of few hours over a certain period. During such periods of days to a few weeks the patients are unable to manage their usual work (case VII, 6, 11).

The fertility of the patients is the same as for the general population, as illustrated by the spread of the Swedish branch of the family (*Gamstorp*).

Inheritance

In the sibships with a risk of affection with periodic adynamia we found 15 affected among a total of 29. Thus, the *Mendel*ian ratio of 0.5 agrees with the hypothesis of regular dominant inheritance with full manifestation within both sexes. The preliminary results from the Swedish branch of the family are in the main identical with ours.

Genetic hygiene

Periodic adynamia will seldom be so severe as to warrant eugenic measures. We have had no case of adynamia in our genetic consultation; but we should never advise against begetting offspring because of the risk of this disorder.

"*Sporadic*" *cases of periodic paralysis*

A large number of seemingly "sporadic" cases of transient muscular paralysis, uncomplicated by other diseases, have been reported in the literature. In many of these very extensive family investigations have been carried out, which preclude, with a rather high degree of certainty, secondary cases among the near relatives. 6 "sporadic" cases have been found so far in this country; and no secondary cases could be demonstrated, despite extensive investigations, comprising several hundred family members.

However, in some of the cases reported earlier the family investigations have obviously not been sufficiently thorough, and secondary cases have repeatedly been disclosed by a subsequent follow-up. This is also true of the Danish investigations. Our patient VI, 5, 2 with family periodic paralysis was quite recently brought to our attention by a hospital. Neither the patient nor his near relatives (both parents are alive) had any knowledge of similar cases in their families. After renewed intensive archive studies we suc-

ceeded in finding a relationship between the family of the patient's father and the great-grandfather of one of our other propositi. For this patient the family investigation had already been carried out as far back and as far into the sidelines as the Danish registers permit, without the branch of the family having been traced in which the new case appeared.

In the majority of the "sporadic" cases, those from the literature as well as the Danish ones, the clinical picture accords closely with that of family periodic paralysis. However, in a few instances certain atypical features suggest a different pathogenesis. One case, described by *Gillespie* [1937], displayed features resembling the picture described by us as family periodic adynamia.

Thus, the existence of sporadic cases of periodic paralysis cannot be excluded.

Concluding remarks

The majority of the familial cases of transient muscular paralysis reported in the literature seem to be of the same type as our cases of hereditary periodic paralysis, judging from the four diagnostic criteria mentioned earlier in this paper:

1. The clinical manifestation of the attack.
2. The potassium disturbances and in relation to this:
3. The favorable response to treatment with potassium.
4. The mode of inheritance, which seems to be that of irregular dominance with sex-limitation to males.

The reports from the literature do not allow of exact calculations regarding the mode of inheritance, because the pedigrees rendered by the authors often are very incomplete. However, a rough estimate may be of some interest, although it is obviously invalidated by the lack of information on the ages of relatives, which doubtless implies a gross error, considering the length of the manifestation period.

Of the 108 propositi of this type reported in the literature 98 were males and 10 females. These propositi had a total of 69 affected parents (41 males and 28 females). All the female propositi belonged to families in which two or more successive generations had affected members. In 36 families, where the information on the number and sex of the sibs seems complete, the propositi had a total of 82 brothers and 81 sisters. Of these, 35 males and 25 females were affected. These figures are in accordance with the hypothesis of irregular dominance with a higher rate of manifestation in males.

Among the cases published of hereditary transient paralysis we have found a few with a picture which seemed analogous, genetically, clinically and biochemically, to that of periodic adynamia: Kulneff's family has already been mentioned—it is possibly a third branch of family VII. Further, *Schoenthal* [1934], *Ecker* [1953] in the United States, and *Buzzard* [1901] in England have described families with frequent attacks of short duration, beginning at an early age.

Occasionally failing improvement after treatment with potassium salts is mentioned in the reports. All these families presented regular dominant inheritance of the disorder, just as in our family VII. We are aware of the possibility that a kinship may exist between the Scandinavian and the American cases described, the more so because several relatives of the ancestors of family VII have emigrated to the USA. But we have been unable to demonstrate such a relationship.

The majority of the cases published thus seem to fit very well into one or the other of the two subgroups described in the present paper. However, a few families have been reported which present all the clinical signs of family periodic paralysis, but at the same time completely regular dominant inheritance, as in family periodic adynamia (*Gaupp* [1940]).

It is impossible to say whether these cases constitute a separate clinical entity. More refined methods of disclosing the basic disturbances underlying the transient muscular paralysis will, perhaps, in future permit of a further division of the syndrome, as it has now been divided into two ethiologically distinct subgroups.

Summary

All the families known in Denmark with transient hereditary paralysis have been investigated.

Genetically and clinically they fall in two distinct groups: 6 families with the well-known picture of family periodic paralysis and one presenting a picture termed family periodic adynamia.

Family periodic paralysis is characterized by severe attacks of muscular paralysis lasting 2–3 days. Hypopotassemia is found during the attacks, which accordingly are relieved by administration of potassium salts. Genetically the disease shows irregular dominant inheritance.

Family periodic adynamia is characterized by less severe attacks, usually lasting less than one hour. Hyperpotassemia may be

found during the attacks, and administration of potassium will produce an attack. Family periodic adynamia is inherited as a regular dominant character.

The literature has been reviewed, and it is suggested that the overwhelming majority of the families described fall within one of these two categories; but more refined clinical and biochemical studies may lead to a further subdivision.

Résumé

Toutes les familles connues au Danemark comme atteintes de paralysie héréditaire transitoire ont été examinées.

Au point de vue génétique et clinique, elles entrent dans deux groupes distincts: 6 familles présentent le tableau bien connu de la paralysie périodique familiale et une, le tableau désigné sous le terme d'adynamie familiale périodique.

La paralysie familiale périodique se caractérise par des accès sévères de paralysie musculaire durant deux à trois jours. L'on peut observer une hypopotassémie aus cours de ces crises qui, par conséquent, sont atténuées par l'administration de sels de potassium. Au point de vue génétique, la maladie montre une hérédité dominante irrégulière.

L'adynamie périodique familiale est caractérisée par des accès moins sévères, qui durent généralement moins d'une heure. Au cours de ces crises, on peut trouver une hyperpotassémie et l'administration de potassium peut déclencher un accès. Cette affection se transmet d'une façon dominante régulière.

Il ressort d'une revue de la littérature que la majorité écrasante des familles décrites appartient à l'une des deux catégories; des études cliniques et biochimiques plus poussées conduiront probablement à une classification plus détaillée.

Zusammenfassung

Die Verfasser haben alle ihnen bekannten dänischen Familien mit erblicher, transitorischer Paralyse untersucht. Erbbiologisch und klinisch bilden diese Familien zwei getrennte Gruppen: sechs Familien zeigen das klassische Bild von familiärer, periodischer Paralyse, während eine Familie ein Bild zeigt, das von den Verfassern als familiäre, periodische Adynamie bezeichnet wird.

Wichtigste Charakteristika dieser zwei Syndrome:

Bei der Paralyse findet sich eine Anfallsdauer von zwei bis drei Tagen, Hypokaliämie während des Anfalls und Bekämpfung mittels Kalium. Dieses Syndrom zeigt einen unregelmäßig-dominanten Erbgang.

Bei familiärer Adynamie übertrifft die Dauer des Anfalls selten eine Stunde. Erhöhte Serumkaliumwerte finden sich oft während des Anfalls, Kaliumverabreichung vermag einen Anfall hervorzurufen. Der Erbgang ist einfach dominant.

Die in der Literatur veröffentlichten Fälle von transitorischen Paralysen wurden nachgeprüft; die meisten scheinen einer dieser zwei Gruppen anzugehören.

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Addendum. In the full report of the Swedish investigations, referred to in this paper, which has now (May 1956) been published, *Gamstorp* has made a small change in the name of the disease, which she calls *Adynamia Episodica Hereditaria.*

Authors' address: Dr. H.Fr. Helweg-Larsen,
Dr. M. Hauge, Dr. Uffe Sagild,
University Institute for Human Genetics,
Tagensvej 14, *Copenhagen* (Denmark).

Libri

U. Teodori, A. Borgi e *G.G. Neri Serneri:* **Eredità e localizzazioni morbose.** Edizioni «Omnia Medica», Pisa 1955. 246 pag. Lit. 2000.

According to the introduction to this book it has been written to utilize the bibliographical material assembled for an invited paper on "Aspects of the problem of the localization of diseases", read before a Congress of Internal Medicine, and to deal, at the same time, more extensively with the rôle played by "heredity" in some frequent diseases of great interest to the internist.

So we find 7 chapters (each with its own summary and bibliography, which makes the search for references rather painstaking) in which status dysraphicus, asymmetries, infectious diseases, allergy, rheumatism and allied conditions, hypertension and arteriosclerosis and tumours are dealt with in this order. The first chapter is a more general one in which an attempt has been made to define the relations between modern concepts of human genetics and old ideas, like "constitution", "biotipologia", "diathesis", or, as the authors say, "the science of the constitutions" (la dottrina delle costituzioni).

The authors have collected a large body of information from the literature which many physicians may find useful. I do not intend to scrutinize each chapter sorting out the useful information from among the many questionable statements. So *e.g.* a regrettable feature of the book is its emphasis on twin research without a critical evaluation of the limitations and biases of this method.

My personal conviction is that attempts of synthesis resulting in books like this one should not be encouraged. A few examples may explain why.

In the closing paragraph of the book the authors say: "(human heredity) ... is an open field for useful research work, which requires a good knowledge of general genetics and of the clinical aspects of the diseases one wants to study ...". Unfortunately the authors' knowledge of genetics, judging from the present book, does not seem up to date.

They seem to ignore that recently human genetics has been provided with several valuable books (*e.g.* those by *Stern*, *Penrose*, *Neel* and *Schull*) and that the "Handbuch der Erbbiologie des Menschen" by *Just* and *Bauer* and the "Human Genetics" by *Gates* are more or less out of date. Concerning experimental genetics the authors refer mostly to well-known classical works but the references appear haphazardly chosen. Describing for instance the pseudo-tumours in *Drosophila* as an example of "hereditary" tumours, only two papers by *Stark* [1918 and 1937] are quoted and the many important recent contributions are ignored. Incidentally, an Italian team (*Barigozzi* and co-workers) is working on those problems.

But what has puzzled me more is to learn that *J. B. S. Haldane* has made "ingiustificate e inopportune critiche, non sempre serene" regarding the "concezione ereditaria" of cancer. I imagined I had a fairly good knowledge of the papers of *Haldane* (at least of the scientific ones) so I rushed to the references list of this chapter. Here I found the following quotation: *Haldane, J. B. S.*, Ann. Eugen. Rev. 7, 28, 1936, which should be a reference to the well-known paper on "A search for incomplete sex-linkage in man", published in the Annals of Eugenics 7, 28, 1936. Perhaps this is quoted because xeroderma pigmentosum is treated in the same chapter, but, alas, where is then *J. B. S. Haldane*'s "unjustified and inopportune criticism" of the "hereditary concept" of cancer ?

M. Fraccaro, Uppsala

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